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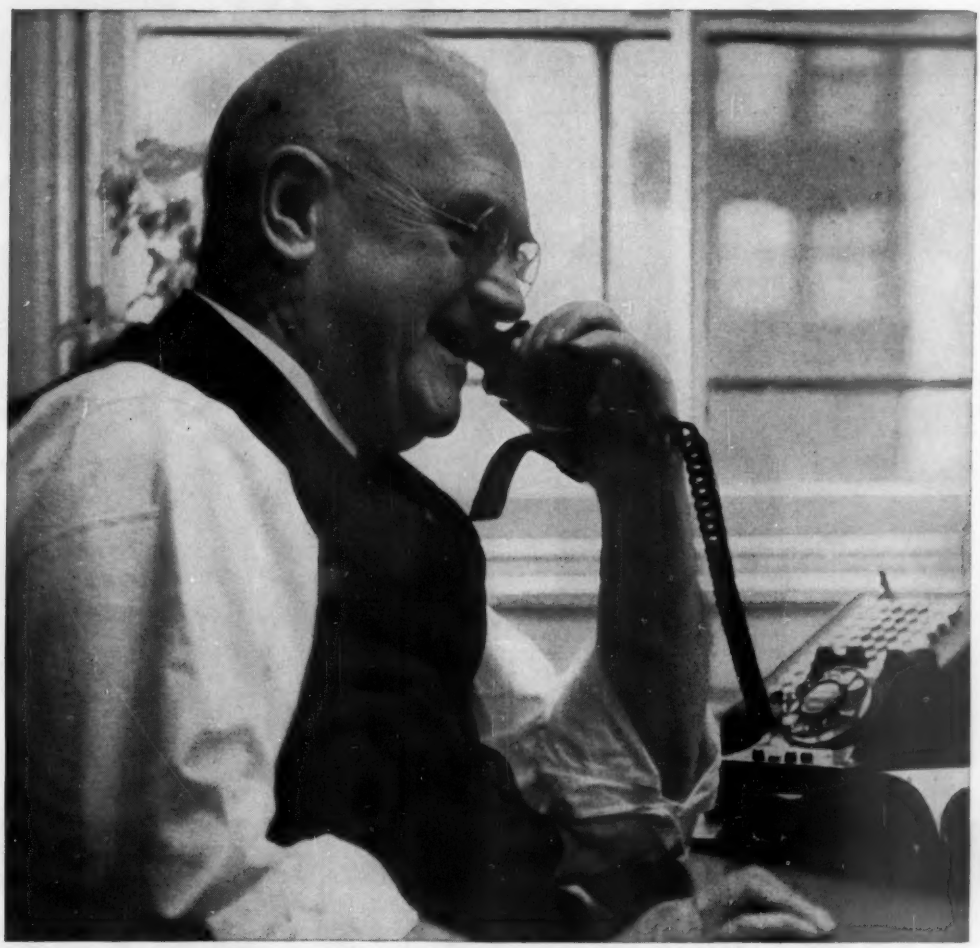

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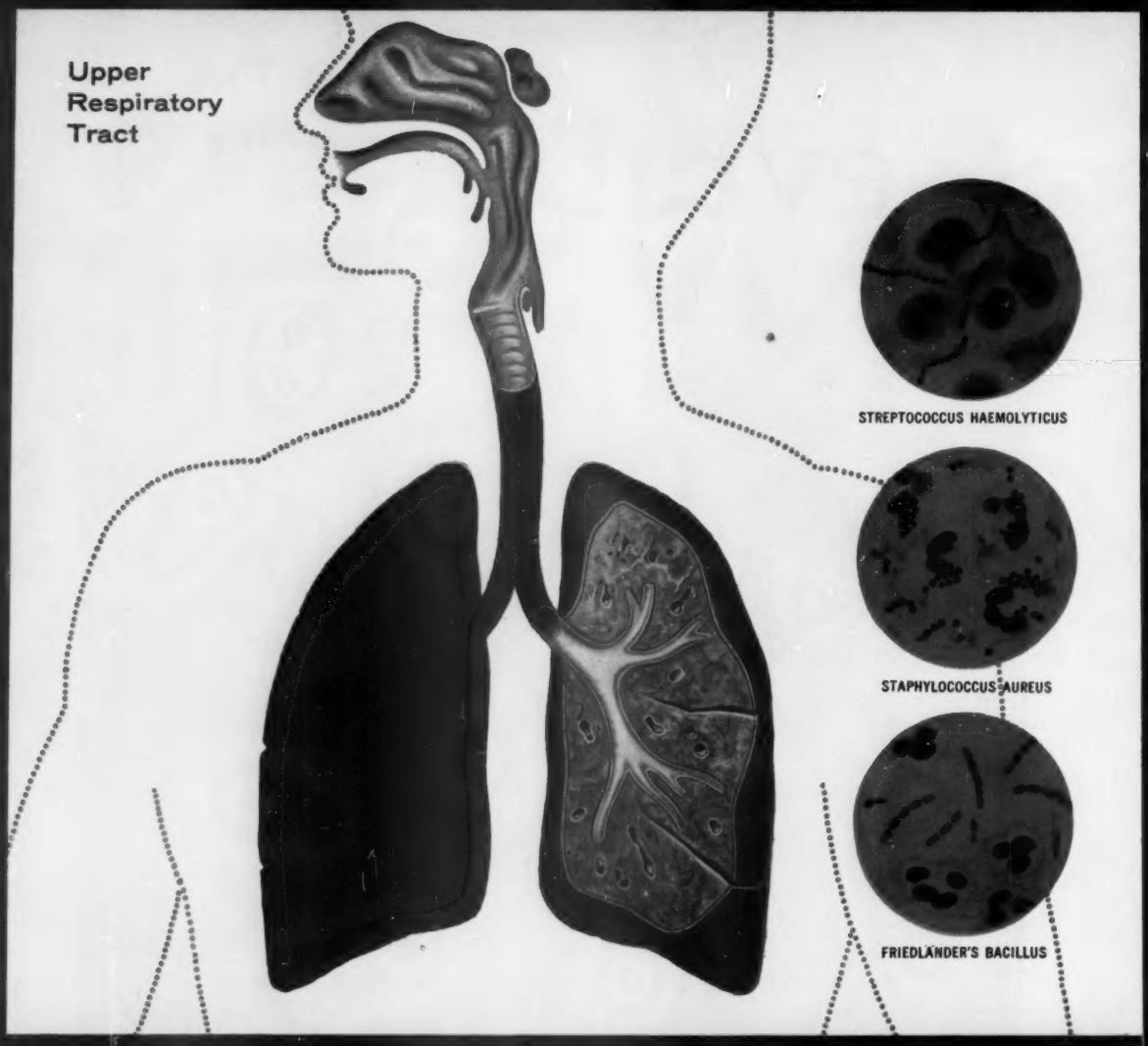

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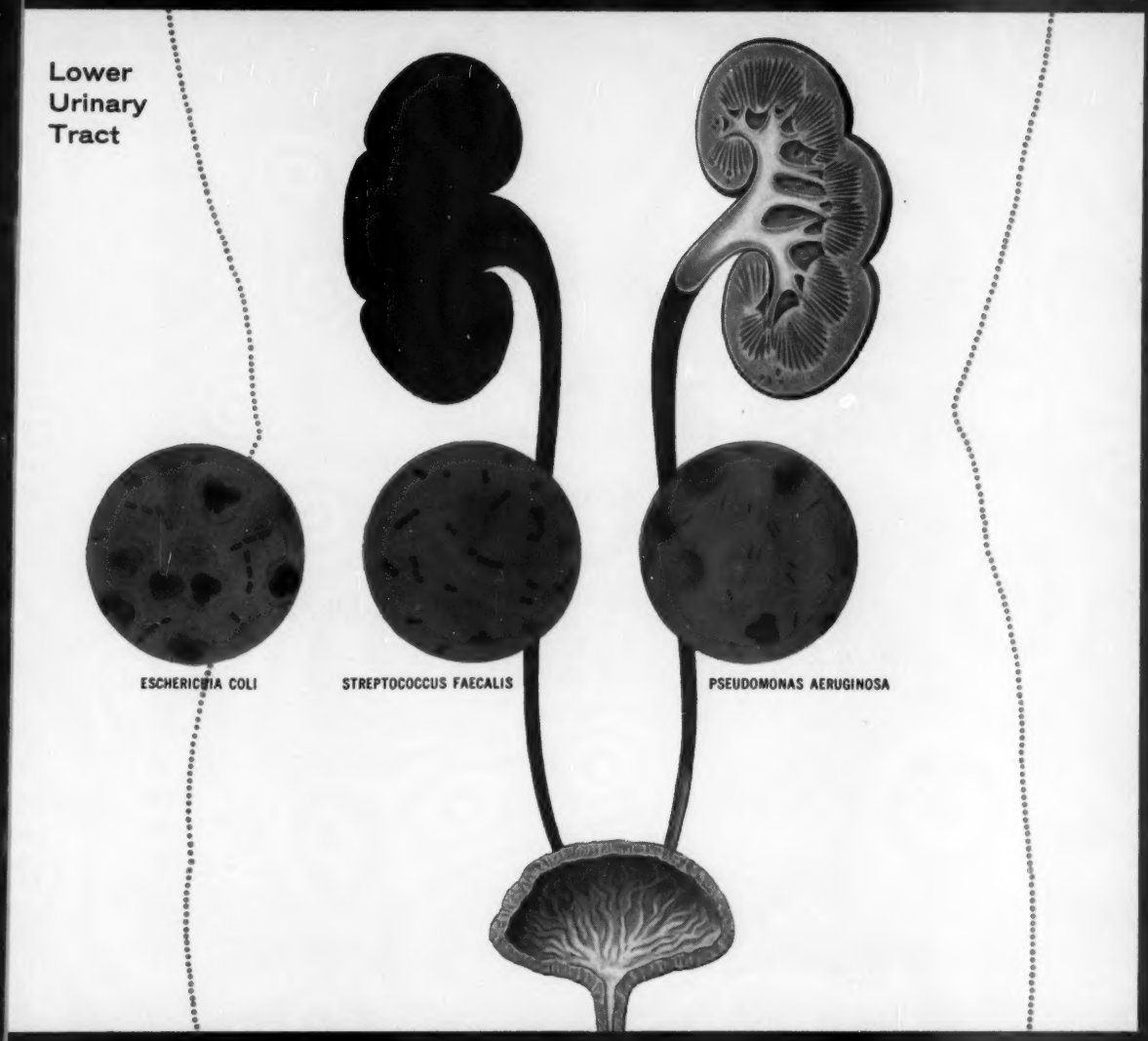

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1. Daly, J. W.: Antibiot. & Chemo. 4:687 (June) 1954. 2. Spink, W. W.: J.A.M.A. *152*:585 (June 13) 1953.

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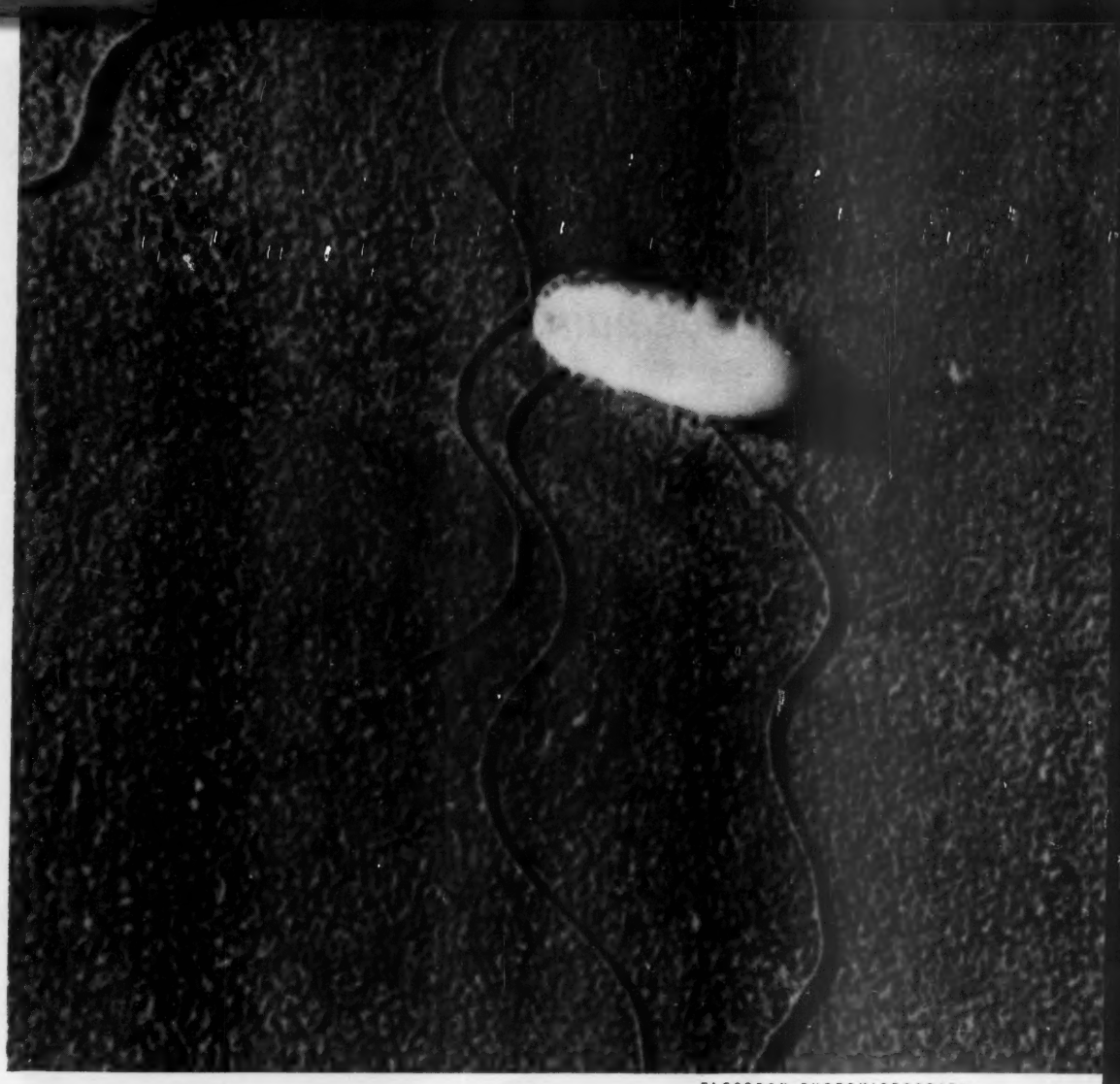

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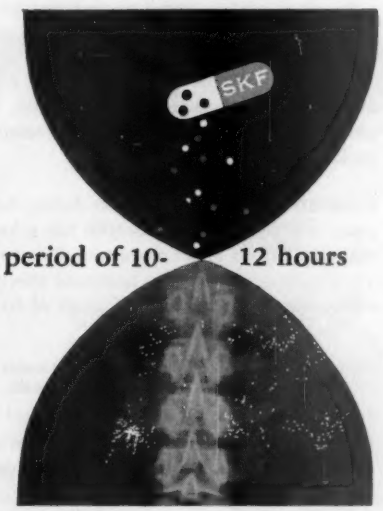

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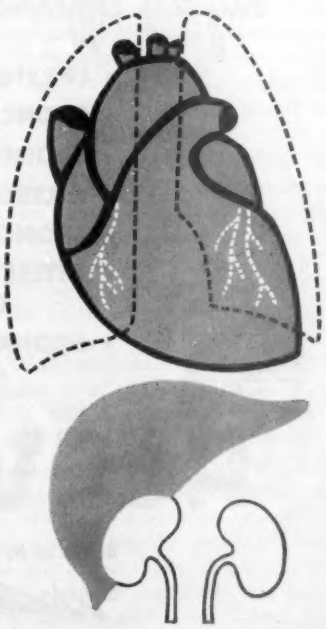

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Volume 252 JANUARY 27, 1955 Number 4

CONGENITAL HEART DISEASE AMONG MENTAL DEFECTIVES AND AN ASSESSMENT OF CARDIAC SURVEY METHODS*

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AUGUSTA, GEORGIA

THE frequency of congenital and acquired heart disease has been investigated by a variety of methods in many different population groups, but mental defectives have not received comparable attention. Mautner[1] recently made a clinical study at a state institution, but confined his observations to mongolism and gave no figures of prevalence.

The purpose of the present study was to assess the over-all frequency of heart disease in mental deficiency with particular reference to the presence of congenital lesions. We were also interested in the occurrence of congenital heart disease among persons with different types of mental retardation, especially mongolism, because of the wide variations reported in this group. An attempt was also made to ascertain if a pattern of associated anomalies existed among the cases of congenital heart disease. Finally, because of the difficulties encountered in surveying such a large group for heart disease, we have analyzed the relative values of the technics used for case detection in this series.

MATERIALS

This study was made at the Georgia Training School, an institution for mental defectives operated by the State at Gracewood, Georgia. During the period of the survey, 723 patients ranging from newborn infants to persons sixty-three years of age were available for study. The age distribution is presented in Figure 1. Forty-nine per cent were males; 51 per cent were females. All patients were white, and there were very few of Jewish or Mediterranean extraction. Table 1 shows the distribution according to type of mental deficiency. The classification used is standard.[2] These diagnoses were made from the history, observations from the referring physicians, physical examinations and a standard intelligence test.

*From the departments of Medicine (Cardiology) and Physiology, Medical College of Georgia.

Aided in part by an undergraduate training grant from the National Heart Institute, and a research grant to the Department of Physiology from the National Institutes of Health.

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METHODS

In determining the methods to be used in this study, history was considered to be of little help because of the time involved and the nature of the group being examined. As a first step, a rapid physical examination of each patient was made, with particular emphasis on cyanosis, clubbing, chest-wall deformity, thoracic pulsation, murmurs, thrills, tachycardia and femoral-artery pulsations. Blood pressures were taken in any case in which the femoral arteries were difficult to palpate, and in all adolescents and adults. Patients with suspicious findings according to the criteria listed above were marked for detailed examinations. Murmurs, regardless of intensity, were regarded as a suspicious finding; 91 patients were selected in this manner, and a 12-lead electrocardiogram and a 6-foot teleroentgenogram were obtained in each. These patients were then subjected to a much more detailed physical examination, with particular emphasis on careful auscultation employing the usual methods for eliciting faint murmurs. Fluoroscopic examination was carried out in 72 of this group, 36 of whom were considered to have some form of cardiovascular disease. No diagnoses were made without the benefit of the 12-lead electrocardiograms, fluoroscopic study, x-ray film of the chest and detailed physical examination.

During the survey, a 4-lead electrocardiographic system suitable for survey work was developed, and this type of electrocardiogram was obtained on all 723 patients. This method consists of Leads 1, aVF and two V leads: "V anterior," placed between Leads V_1 and V_2 in the center of the sternum at the level of the fourth interspace, and "V lateral," in the same horizontal line in the midaxilla, approximately 1 interspace above the usual position of Lead V_6. The accuracy of this system compares favorably with that of the routine 12-lead electrocardiogram.[3]

The criteria for hypertrophy of the right, left and both ventricles were adapted for the 4-lead system from the well controlled studies of others.[4-7] The only change in criteria from the previously reported study was that the upper limits of normal for the "sum of the left-ventricle potentials" was increased to 35 mm. (standardization: 1 mv. equals 1 cm.).

This was done because more extensive experience has shown that a normal adult occasionally has voltages within this range. The number of cases with left-ventricle potentials greater than 33 mm. (previous maximum) would have added considerably to the burden of the resurvey of patients with "abnormal voltages." As pointed out below, this expansion of the normal range seems clearly justified in view of the large number of false-positive tracings even with the new criteria. Seven cases of heart disease that would not have been detected by the x-ray or clinical survey were found by the mass electrocardiographic technic.

This group of patients offered a particularly rigid test for the electrocardiographic method of survey for the following reasons:

Many of the patients were unco-operative, and it was sometimes difficult to obtain technically good records.

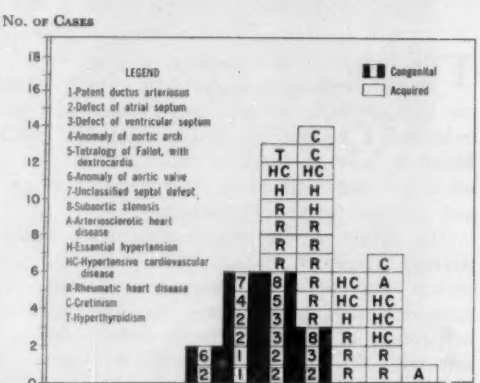
There was a high prevalence of spinal and chest-wall deformities, which tended to distort the electrocardiogram.

There were many children in whom the previously established adult criteria for normality would not necessarily apply.[8]

Many of the patients, although chronologically in the adult age range, had small, infantile bodies, and it was difficult, therefore, to know what voltages should be considered abnormal.

Through the co-operation of the State Department of Public Health, it was possible to obtain 70-mm. x-ray films of the chest on all patients who were able to stand (approximately 680). One patient with congenital heart disease was unable to co-operate. Eighteen of these films were considered to be suspicious for heart disease by the Division of Tuberculosis Control, State Department of Public Health. Fourteen patients had not been suspected previously, and were subjected to the detailed examination, including the 6-foot teleroentgenograms and 12-lead electrocardiograms described above. Three cases of heart disease were added from this group. All films were then reread by us, and 61 cases were regarded as suspicious. Seven of these patients were already known to have heart disease, but an additional 4 cases of heart disease were detected. We deliberately "over-read" these x-ray films and deliberately noted findings that ordinarily would not have been considered pathologic but were, in our opinion, "slightly suspicious." This was considered to be justified since the primary purpose of the study was to detect as accurately as possible the frequency of heart disease and not, per se, to test the efficiency of any method of survey or our ability to have the fewest number of false-positive readings. Moreover, the interpretation of these films was unusually difficult for the same reasons that have been listed as causing uncertainties with the electrocardiograms.

To obtain a conservative estimate of the prevalence of heart disease, great care was taken not to overdiagnose, and it was thought that since several patients who were not definitely known to have heart disease and could not be fitted well into a diagnostic category were not included in the tabulation of results, the frequency as reported here is probably on the low side. It was not thought feasible under the circumstances to perform cardiac catheterization or angiocardiography, which would undoubtedly have enabled some improvement or corrections in diagnoses. It is believed, however, that the diagnoses as



Age Group	0-1	2-4	5-10	11-15	16-20	21-30	31-40	41-50	51-63	TOTAL
Patients in Group	4	7	60	178	176	196	60	39	3	723
Congenital (%)	0	0	33	3.3	2.3	1.5	0	0	0	2.35
Acquired (%)	0	0	0	0	4.0	5.5	10.0	17.9	33.3	4.43

Figure 1. *Relation of Cardiovascular Disease to Age.*

recorded are well established on clinical grounds and represent our fairly extensive combined experience in the diagnosis and treatment of congenital heart disease. For a rough assessment of the validity of the diagnoses, however, a few words of explanation are necessary. The diagnoses of defect of the atrial septum were based on a pulmonary systolic murmur of various degrees of intensity, incomplete right-bundle-branch block in 5 and pattern of hypertrophy of the right ventricle in the sixth, enlarged and pulsatile pulmonary-artery segments and evidence of hypertrophy of the right ventricle by fluoroscopy. All 3 defects of the ventricular septum were accompanied by thrills and loud murmurs of Grade 4 or greater intensity in the left parasternal line in the third or fourth interspace, electrocardiograms either normal or showing slight hypertrophy of the left ventricle and x-ray silhouettes that were relatively normal. The 1 patient with an unclassified septal defect showed pulsatile and engorged lung fields, but the murmur and the electrocardiogram did not clearly differentiate atrial and ventricular defects. Both patients with patent ductus had typical machinery murmurs. The anomaly of the aortic arch was a right aortic arch with persistent left root, with pathognomonic x-ray findings.[9] Both cases of subaortic stenosis showed the characteristic

murmur with a well preserved aortic second sound and mild to moderate enlargement of the left ventricle. The anomaly of the aortic valve was in a six-year-old child with a loud murmur of aortic insufficiency at least since the age of three (when admitted to the institution). She had no other murmurs, but had fluoroscopic evidence of mild enlargement of the left ventricle. The single patient with dextrocardia was intensely cyanotic, had clubbing of the fingers, a normal over-all heart size but with enlargement of the right ventricle, and normal or slightly ischemic lung fields without pulsation, and had attained the age of twenty-six without the development of congestive heart failure. The additional diagnosis of tetralogy of Fallot was made on the basis of these findings.

The cretins exhibited classic systemic manifestations of this disease and had massive cardiac enlargement. All patients with rheumatic heart disease, with 4 exceptions, had characteristic auscultatory findings of combined disease of the aortic and mitral valves. These 4 patients had faint murmurs of aortic insufficiency and presented no evidence of other valvular deformity. Any of these may also be a congenital deformity of the aortic valve — for example, a bicuspid or fenestrated aortic valve producing insufficiency. Since the duration of these murmurs was not known and all patients were adolescents or older, it was thought that the conservative course would be to classify them as acquired heart disease. The patients with the diagnosis of hypertensive cardiovascular disease had diastolic pressures of over 100 at one time or another and enlargement of the left ventricle as evidenced by either fluoroscopic or x-ray study. The 4 patients with essential hypertension had similar blood-pressure findings, but no clinical evidence of cardiac involvement. In 1 case of arteriosclerotic heart disease electrocardiographic and historical evidence of a myocardial infarction was subsequently verified at autopsy. The other showed enlargement of the left ventricle, widening of the aorta and a well defined plaque of calcium in the ascending aorta. The case of hyperthyroidism was one of classic Graves's dis-

TABLE 1. *Distribution of Heart Disease According to Type of Mental Deficiency.*

MENTAL DIAGNOSIS	NO. OF PATIENTS	CASES OF CONGENITAL ORIGIN	CASES OF ACQUIRED ORIGIN	TYPE OF HEART DISEASE
Imbecility (neurosyphilis)	1	0	0	
Imbecility (endocrine, unclassified)	2	0	0	
Idiocy (familial)	3	0	0	
Microcephaly	3	0	0	
Idiocy (postinfectious)	4	0	0	
Cranial anomaly	4	1(25%)	0	Defect of ventricular septum (1)
Hydrocephalus	5	0	1(20%)	Rheumatic heart disease (1)
Idiocy (post-traumatic)	4	0	0	
Idiocy (epileptic)	5	0	0	
Cretinism	3	0	3(100%)	Myxedema heart (3)
Moronism (post-traumatic)	6	0	0	
Moronism (epileptic)	11	0	0	
Idiocy (undifferentiated)	13	2(15%)	0	Defect of atrial septum (1); anomaly of aortic valve (1).
Moronism (postinfectious)	11	0	0	
Imbecility with epilepsy	22	0	0	
Unclassified	24	0	0	
Imbecility (postinfectious)	33	0	1(3.3%)	Hypertensive cardiovascular disease (1)
Imbecility (post-traumatic)	35	0	2(5.7%)	Hypertensive cardiovascular disease (1); rheumatic heart disease (1).
Cerebral palsy	35	0	0	
Moronism (undifferentiated)	45	0	2(4.4%)	Arteriosclerotic heart disease (1); essential hypertension (1).
Mongolism	86	6(7%)	2(3.5%)	Rheumatic heart disease (3); defect of atrial septum (3); patent ductus arteriosus (1); defect of atrial septum (2).
Imbecility (undifferentiated)	108	3(2.8%)	5(4.6%)	Rheumatic heart disease (2); essential hypertension (1); arteriosclerotic heart disease (1); defect of atrial septum (1); tetralogy of Fallot, with dextrocardia (1); unclassified septal defect (1); hypertensive cardiovascular disease (1).
Imbecility (familial)	124	2(1.6%)	9(7.4%)	Rheumatic heart disease (4); hypertensive cardiovascular disease (3); anomaly of aortic arch (1); defect of ventricular septum (1).
Moronism (familial)	136	3(2.2%)	7(5.1%)	Essential hypertension (2); hyperthyroidism (1); defect of atrial septum (1); defect of ventricular septum (1); rheumatic heart disease (4); patent ductus arteriosus (1).
Totals	723	17(2.35%)	32(4.42%)	
Omitting cases of mongolism	637	11(1.57%)	30(4.15%)	

ease and the patient responded well to thyroidectomy.

Results

Table 2 lists by diagnoses the cases of congenital and acquired cardiovascular disease, with the percentage of both types as applied to the population as a whole (723 patients). The percentage for acquired disease has been calculated with and without the inclusion of the 4 cases of essential hypertension and the 3 cretins.

TABLE 2. *Types of Cardiovascular Disease.*

Congenital Disease	No. of Cases	Acquired Disease	No. of Cases
Defect of atrial septum	6	Cretinous heart disease	3
Defect of ventricular septum	3	Rheumatic heart disease	15
Septal defect, unclassified	1	Hypertensive cardiovascular disease	7
Patent ductus arteriosus	2	Essential hypertension	4
Anomaly of aortic arch	1	Arteriosclerotic heart disease	2
Anomaly of aortic valve	1	Hyperthyroidism with cardiac involvement	1
Subaortic stenosis	2		
Tetralogy of Fallot & dextrocardia	1		
Totals	17(2.35%)		32(4.42%)
Total cardiovascular disease			49(6.77%)
Omitting essential hypertension			45(6.22%)
Acquired heart disease omitting essential hypertension			28(3.87%)
Omitting essential hypertension & cretinism			25(3.46%)

Table 1 presents the distribution of the individual cases of both congenital and acquired heart disease among the different diagnostic types of mental defectives. The percentages, of course, mean very little in groups in which the number of cases is small. It will be noted that the percentage of congenital heart disease is highest among patients with mongolism, but if the 86 mongoloid patients are subtracted from the total of 723 patients the frequency of congenital heart disease is still 1.57 per cent. Since mongolism is of particular interest, Table 3 lists the age distribution and cardiac diagnoses of patients.

TABLE 3. *Heart Disease in Mongolism (According to Age).*

Age	No. of Patients in Group	No. with Heart Disease	Type of Heart Disease*
yr.			
<1	2	0	None
1-4	1	0	None
5-10	11	1	Defect of atrial septum (1)
11-15	14	1	Patent ductus (1)
16-20	8	3	Rheumatic (1); defect of atrial septum (1); subaortic stenosis (1).
21-30	33	2	Defect of atrial septum (1); subaortic stenosis (1).
31-40	13	2	Rheumatic (2)
41-50	4	0	None
Totals	86	9	

*Frequency: total, 10.4 per cent; congenital, 7.0 per cent; & rheumatic, 3.5 per cent.

Figure 1 shows the distribution of heart disease by ages and points out the declining frequency of congenital heart disease with increasing age as well as the steady high climb in that of acquired. Since there were only 11 patients below the age of five, the absence of congenital heart disease in these groups is hardly significant.

Figure 2 presents the number of cases picked up by the 57 suspicious 70-mm. x-ray films, the 76 "abnormal" 4-lead electrocardiograms and the total number of cases picked up by either method in the 128 patients who showed an abnormality on either x-ray or electrocardiographic examination. The block graph on the extreme right of this illustration demonstrates

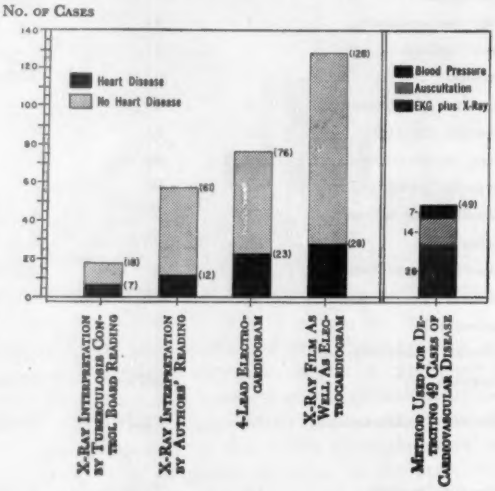


FIGURE 2. *Methods of Detection in 49 Cases of Cardiovascular Disease.*

that 14 cases (27 per cent) would never have been detected if the auscultatory findings had not been noted. Seven more (14 per cent) would not have been detected if the blood pressures had not been measured. The latter group, of course, included the 4 cases of essential hypertension. It must be pointed out that in some cases in which mass survey x-ray and electrocardiographic findings were interpreted as normal, 12-lead electrocardiograms and the reading of the full 14-x-17 chest film with a high index of suspicion did suggest that the patient had heart disease.

Figure 3 is a graphic representation of the relative efficiency of the electrocardiographic and x-ray diagnoses applied to the 4-lead electrocardiogram and the 70-mm. roentgenogram. It will be noted that the aortic arch could not be identified as being on the

left in 13 cases, but in only 1 of these was the diagnosis of right aortic arch substantiated by fluoroscopy with barium swallow. As a matter of fact, x-ray films in some patients without the right aortic arch were much more suggestive of this anomaly than the film in the 1 case in which it was present. The x-ray appearance of a large pulmonary artery did not indicate heart disease in 9 of 10 cases; the single case of heart disease was a defect of the atrial septum, but this would have been picked up by the electrocardiographic survey method anyway. One case of apparent dextrocardia also presented an unusual fluoroscopic picture. A few degrees of rotation from the straight anteroposterior view would certainly have given the appearance that most of the heart was in the right side of the chest. The electrocardiogram did not confirm the diagnosis of dextrocardia, and since no specific diagnosis could be made, this was not included among the cases listed as heart disease, although it is possible that it was actually a bizarre congenital anomaly. Almost a third of the patients suspected of having hypertrophy of either the right or the left ventricle or both actually turned out to have heart disease.

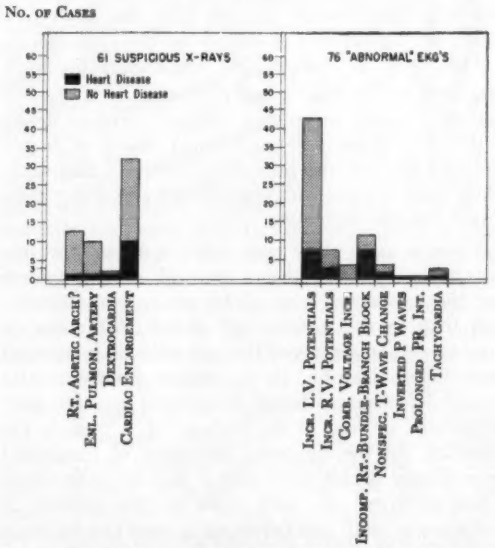


FIGURE 3. *Efficiency of Various X-Ray and Electrocardiographic Interpretations.*

The most striking point about the readings of the 4-lead electrocardiogram is the number of false-positive interpretations when an increase in left-ventricle potential was considered an abnormal finding. These patients did not have a prolonged ventricular activation time, and the ST-segment or T-wave changes characteristic of hypertrophy of the left ventricle were not observed. An increase in both right-ventricle and left-ventricle potentials in the same case was also disappointing since in no case did it actually appear to represent combined ventricular hypertrophy. About two thirds of the patients with incomplete right-bundle-branch block, and half those with isolated T-wave changes, however, had heart disease.

That the number of cases of high left-ventricle voltage without heart disease is not simply an artifact of the 4-lead electrocardiographic method is shown by the fact that, when 43 such cases available were rechecked by a repeat 4-lead and a complete 12-lead series, 10 (and not always the same 10) demonstrated the same phenomenon on 12 leads, and 17 on the repeated 4-lead tracing. Actually, 25 of the 43 12-lead rechecks indicated abnormal electrocardiograms of one sort or another. These results are brought together in Table 4. The discrepancy between these three tabulations did not surprise us since, when one is reading an electrocardiogram according to strict measurement criteria, daily differences in electrode placement often throw a case considered just within normal limits on one day into the abnormal group on the next day or vice versa. The frequent failure of this type of electrocardiographic interpretation, which eliminates the aids of clinical judgment and knowledge of the patient, illustrates once again the necessity of having this help for correct evaluation.

TABLE 4. *Results of Repeat 43 "Abnormal" 4-Lead Electrocardiograms in Patients with No Heart Disease.*

Abnormality	4-Lead Electrocardiogram	4-Lead Repeat Electrocardiogram	12-Lead Check Electrocardiogram
Hypertrophy of left ventricle (voltage)	27	17	10
Hypertrophy of right ventricle	3	5	4
Combined hypertrophy (voltage)	4	3	2
Incomplete right-bundle-branch block	4	3	4
Hypertrophy of left ventricle & T-wave change	0	1	0
Nonspecific T-wave change	2	0	1
Prolonged PR interval	1	1	1
Tachycardia (rate greater than 120)	2	3	3
Totals	43	33	25

Careful examination of every case of congenital heart disease for anomalies of other systems revealed no significant pattern in the light of the frequency of such findings as supernumerary nipples and high-arch palates in the institution as a whole. This confirms the conclusions of a previous study.[10]

Discussion

It has been difficult to find studies of comparable nature on a population with similar age distribution without mental deficiency. The bulk of the evidence concerning the expected prevalence of congenital heart disease, however, supports the contention that it is seven or more times higher among this group of mental defectives than in the general population.

Table 5 summarizes selected studies that are of particular interest in this regard. One striking area of agreement among all previously reported attempts to find the frequency of congenital heart disease and the present study is the decreasing occurrence of these anomalies with age.[10] This is true both in clinically and in pathologically studied series. Figure 1, which relates the cases of congenital and acquired heart disease to age in our series, shows a striking and surprisingly consistent decrease in congenital heart disease as age increases. The oldest patient with congenital disease in our series was twenty-three years of age. The same chart reveals a consistent climb in frequency of acquired heart disease with increasing age; the small number of patients among the very young and very old, of course, makes the exact percentages untrustworthy in these groups. From the series listed in Table 5, there appears to be remarkable agreement about the prevalence of congenital heart disease among adults and older children. This appears to be something less than 0.3 per cent when determined by various clinical methods. A particularly good comparison seems possible with the series of Rauh[13] among patients five to nineteen years of age, with a frequency of 0.27 per cent. We had 414 patients in this age group, and 14 cases of congenital heart disease appeared among them (3.38 per cent).

TABLE 5. *Occurrence of Heart Disease in the General Population.*

SOURCE OF DATA	DESCRIPTION	FREQUENCY OF CONGENITAL HEART DISEASE	
		IN ENTIRE SERIES	AMONG ALL CARDIAC PATIENTS
		%	%
Living patients:			
Thordarson[11]	Clinical series of 31,771 medical outpatients in Copenhagen	0.27	1.80
Maresh et al.[12]	11,236 6th-grade children surveyed for heart disease	0.27	27.5
Rauh[13]	64,900 children 5 to 19 yr. of age	0.24	44.0
Autopsy series:			
Leech[14]	13,115 autopsies, Johns Hopkins Hospital; 170 cases of congenital heart disease (62 patients under 2 yr. & 54 under 1 yr.).	1.28	
Philpott[15]	7240 autopsies during 10-yr. period:		
	Over-all occurrence	1.17	
	Patients over 2 yr.	0.30	
Gelfman & Levine[16]	34,023 unselected autopsies:		
	Over-all occurrence	1.36	
	Patients over 2 yr.	0.50	
Gibson & Clifton[17]	1950 consecutive autopsies in children:		
	Over-all occurrence	5.40	
	1st mo. of life	11.60	
	1 mo. - 1 yr.	6.30	
	2d year	4.30	
	2d - 5th yr.	3.00	
	6th - 9th yr.	2.90	
	10th - 12th yr.	3.70	

Various figures are given for the prevalence of congenital heart disease at autopsy. Some of these are surprisingly high, but when the autopsies are divided into age groups, it is found that the great majority of congenital heart disease, as would be expected, appears among infants less than two years old. MacMahon et al.,[10] who found the occurrence among live births to be 0.37 per cent, noted that 6 out of 10 died in less than a year. In Leech's[14] series, with an over-all prevalence of 1.28 per cent, more than a third of all patients with congenital heart disease were less than two years of age, and one must conclude that in his autopsied patients over the age of two, congenital anomalies must have represented considerably less than 1 per cent. Philpott's[15] series clearly defines the frequency of congenital anomalies as 0.3 per cent over the age of two but notes an over-all figure of 1.17 per cent. Gelfman and Levine[16] give 0.5 per cent for prevalence of congenital heart disease over the age of two. Figure 1 indicates that only 4 of our 723 patients were under two years of age, and they appeared to have normal hearts. The series of autopsies in children reported by Gibson and Clifton[17] showed a fairly steady decline from the high frequency of 11.6 per cent in infants less than one month old, but even so, their figures are remarkably high compared to the other series reviewed. It is possible that their figures are higher not only because death itself selects those with malformed hearts as in all autopsy series but also because a children's diagnostic center attracts cases with complicated and severe congenital cardiac anomalies.

It seems quite clear even when most autopsy reports are compared with our clinically derived figures that the prevalence is much higher in mental defectives than in the general population. Moreover, it is not known how many of the patients with congenital heart disease described in the various series were also mental defectives, although mongolism was definitely represented in some of the studies.[14,17] A possible explanation for the apparent frequency of congenital heart disease in this institution is the care with which it was surveyed. As such series go, the number of patients was small and permitted a more careful study to be done than when many thousands of patients are investigated. The interest of the investigators was also particularly centered on congenital anomalies. That this may be a factor is apparent from our observation of several pulmonic systolic murmurs, which appeared by the usual auscultatory criteria to be benign, and yet fluoroscopic and electrocardiographic examination indicated the presence of a defect of the atrial septum. It seems to us impossible to evaluate the pulmonic systolic murmur of moderate intensity, which changes with respiration or position, without the benefit of electrocardiographic and x-ray methods, and we are sure that these procedures were not carried out in some of the very large series. On the other hand, we are convinced that even the high prevalence in our study was probably lower than would have

been found at autopsy. Figure 2 vividly demonstrates that a reasonably accurate yield of heart disease in a group depends on careful auscultation, electrocardiography, roentgenology and sphygmomanometry in every case.

One interesting point was driven home with considerable force. We were greatly impressed with the fact that some of the patients who were carefully examined on two or more occasions on one day exhibited no murmur pathognomonic of valvular disease and on another had an aortic or mitral diastolic murmur easily heard by all three observers, although, of course, it might still be of Grade 2 intensity or less. Three cases of isolated aortic insufficiency were missed on at least one occasion by all of us. It is also an interesting commentary that 14 of the 49 cases of cardiovascular disease were in patients with normal blood pressures and survey electrocardiograms and, therefore, could not have been detected at all if careful auscultation had not been done. Fluoroscopy in some of these patients, however, gave abnormal findings.

It is also noteworthy that all types of congenital heart disease, with the possible exception of the tetralogy of Fallot, were relatively simple and usually of good prognosis. It can safely be assumed that among mental defectives dying under the age of two, there was an even higher prevalence of congenital heart disease, and these probably included more complicated types of poorer prognosis. Of all the patients with heart disease, it was surprising that none were or apparently had ever been in congestive heart failure, with 1 questionable exception. All adult cardiac patients, with the exception of the 1 with myocardial infarction, had been doing manual labor at the institution. Most of the patients were quite articulate, and yet none complained of the usual symptoms of cardiac decompensation.

The group of 86 mongoloid patients received special attention, and 12-lead electrocardiograms, as well as the other measures previously referred to, were taken on each. It is also true that our index of suspicion was probably much higher because of our knowledge of the experience of others with this malformation. This may account for the fact that, as a group, those with mongolism exhibited the highest frequency of congenital heart disease (7 per cent). Actually, the 2 mongoloid patients classified as having rheumatic heart disease were included among the 4 cases of isolated aortic insufficiency referred to above and may well have had a congenital anomaly of the aortic valve, which would make the prevalence over 10 per cent. Although either percentage is higher than in the institution as a whole or in any other large mental group it is not nearly so high as one would have suspected from reading the reports of autopsies on mongoloid persons. As pointed out above, the frequency of congenital heart disease at autopsy runs systematically higher than that of clinically diagnosed disease. With the exception of the questions of classification mentioned above, we believe, however, that few if any significant anomalies were missed because of our particularly close attention to this group. We think that the age of the groups studied has much to do with the apparent discrepancy. Only 3 of our 86 mongoloid patients were less than five years of age (Table 3). It is assumed that others with severe congenital heart disease probably died at an early age and that the remaining group, which constitutes our series, survived probably in large part because they did not have a very severe cardiovascular anomaly. This concept gains some support from our limited autopsy experience at this institution. Ten patients have died in the last two years. Three of these were mongoloid, the first, who died at the age of forty, had no heart disease at autopsy. The second, who was nine months of age, had a clinical diagnosis of defect of the ventricular septum, and autopsy revealed, in addition, a patent ductus arteriosus. The third patient, also nine months of age, had a defect of the atrial septum that was also diagnosed clinically. The fact that the only mongoloid adult had no heart disease and that the other 2 were infants and did have congenital anomalies tends to support these conclusions but would, of course, give a very high figure of congenital heart disease among autopsies of mongoloid persons. None of the other 10 patients had congenital heart disease, but 1, included in the present series, had a myocardial infarction. Benda[18] states that 75 per cent of patients with mongolism dying under two years of age have congenital cardiac anomalies; this figure is reduced to 35 per cent among those surviving this age. No evidence for these statements, however, is presented. Over-all statistics collected in a variety of ways, place the prevalence between 16 and 25 per cent.[10] One must conclude that autopsy series of young mongoloids, as in any unselected series of autopsies under the age of two, will yield an extremely high percentage of congenital heart disease. On the other hand, autopsy series of mongoloid adults will give a percentage considerably higher than that in the general population but of much more modest proportions.

If the 86 mongoloid patients are subtracted from the group of 723 patients, the frequency of congenital heart disease among the remaining 637 is 1.57 per cent, which is approximately five times that reported in groups not mentally defective. The distribution of congenital heart disease in various diagnostic groups is presented in Table 1. These cases are found in only 5 other diagnostic categories. Although definite conclusions cannot be drawn because of the small numbers of patients in many of the groups, it is suggestive that the groups listed as postinfectious, post-traumatic and so forth included no cases of congenital heart disease, and the types that probably resulted from intra-uterine malformation did.

The ratio of congenital to acquired heart disease is also interesting: 37.8 per cent of all cases of heart disease in this series were thought to be congenital

(4 cases of essential hypertension are excluded). This is over twenty times the relative prevalence reported by Thordarson[11] among adults (patients over twelve years of age), over twice that described by Maresh et al.[12] (approximately twelve years of age) and slightly lower than that in Rauh's[13] series (five to nineteen years of age). A better comparison of the last statistics is afforded by our own patients of the same age. The frequency of congenital heart disease among these 21 patients was 67 per cent. It is apparent that one must keep in mind the age groups surveyed when comparing over-all figures. Because of the reciprocal relation between the prevalence of congenital and acquired heart disease, so far as age is concerned, it appears that under the age of two, when rheumatic carditis is unusual, almost all cases of heart disease are congenital. The frequency of congenital heart disease falls steadily, however, and represents between 20 per cent and 45 per cent of cardiac patients in the pediatric age group but between 1 and 6 per cent of large series of predominantly adult cardiac patients.[19,20] Although an exact comparison is not possible, it again seems clear that since over 90 per cent of our patients were eleven years or older, the prevalence of congenital heart disease among the total number of cardiac patients of all types is higher than would ordinarily be expected.

TABLE 6. *Patients with Normal 4-Lead Electrocardiographic and 70-mm. X-Ray Readings.*

CARDIAC DISEASE	NO. OF CASES
Defect of ventricular septum	3
Patent ductus arteriosus	1
Subaortic stenosis	1
Anomalous aortic valve	1
Hypertensive cardiovascular disease	6
Essential hypertension	1
Rheumatic heart disease	8
Total	21

Reliable estimates of the prevalence of all types of heart disease in the general population are still lacking.[20] The frequency in this group (6.77 per cent), however, is greater than a considered estimate of 2 per cent for the population as a whole.[20] It is again difficult to arrive at an exact comparison, but if the inordinately high percentage of congenital heart disease in this group is subtracted, the figure of acquired heart disease in this institution is 4.42 per cent. If cretins, who might also be considered to have congenital heart disease, and patients with essential hypertension are subtracted, the frequency is 3.46 per cent. Although there were only 102 patients over the age of thirty in this institution, a glance at Figure 1 reveals a high percentage of acquired disease among these patients. The majority of cases were among familial imbeciles and morons, who apparently have excellent longevity and make up the majority of patients over thirty years of age. This fact explains the high prevalence of acquired heart disease in these diagnostic categories (Table 1).

Finally, we should like to make some comments on the efficiency of various survey methods in detecting heart disease. We found that mass survey x-ray studies were a very poor indicator, and this confirms the experience of others.[21] Even when these films were deliberately over-read, only 12 of 45 cases of heart disease were detected. The 4-lead electrocardiogram was much better, but disclosed only 23 of the 49 cases of cardiovascular disease. It must be admitted, however, for reasons previously discussed, that the normal range of the 4-lead electrocardiogram is probably better defined in adults of normal skeletal frame.[3] The combination of the two methods yielded 28 cases and was, as had been expected, better than either alone. On the other hand, the number of false-positive interpretations in either single or combined methods presented a formidable task to the examiners. One is forced to conclude that any survey method that excludes auscultation and blood-pressure recording may well miss almost half the cases of heart disease in a group. It is important to realize, however, that the rate of detection varies tremendously with the type of heart disease with which the examiner is confronted.[21,22] The 21 cases in which detection depended entirely on blood pressure and auscultatory findings are listed in Table 6.

The difficulties in surveying by auscultation are quite obvious — principally the high frequency of murmurs without heart disease, the fact that many murmurs, even if detected, require x-ray and electrocardiographic examinations for evaluation, the skill required of the examiner and examiner fatigue. We found that the intense concentration required to detect minimal diastolic murmurs, in addition to the assembly-line flow of patients, did not permit the examination of more than 10 or 15 patients in a series without a recess. Even under these conditions, our experience in this survey has taught us that continual restudy of some of the patients would result in an increase in the number of cases of heart disease because of the apparent appearance and disappearance of Grade 1 and 2 diastolic murmurs. Unfortunately, we can present no ready answer to the question of a rapid, efficient method of detecting heart disease in a large group.

SUMMARY AND CONCLUSIONS

The prevalence of acquired heart disease among 723 institutionalized mental defectives was 4.42 per cent, and that for congenital heart disease 2.35 per cent.

Comparison with studies of mentally normal people of similar age groups leads to the conclusion that the percentage of congenital heart disease in this institution is seven or more times that for the general population. Although the evidence is less convincing,

the percentage of acquired heart disease also seems slightly higher than had been expected.

Among the various mental diagnoses, the frequency of congenital heart disease was greatest among mongoloid patients (7 per cent) but even when they were subtracted the prevalence among the remaining patients was several times that expected in the general population.

Although congenital heart disease was quite frequent among mongoloid patients, the often-quoted figure of 50 per cent or more, mainly based on autopsy series and including many patients dying in infancy, does not seem applicable to adults with this condition.

As in other autopsy and clinical series, the prevalence of congenital heart disease falls steadily with increasing age. The frequency of acquired heart disease shows the opposite trend, increasing steadily over the age of fifteen.

All cases of congenital heart disease detected in this predominantly adult population appeared to be defects with a generally good prognosis, and it is suspected that the majority of patients with severe and complicated anomalies among the mental defectives, as in the population as a whole, died in early childhood and before they could be institutionalized.

Aside from the mongoloid defects, all cases of congenital heart disease were grouped in only five other diagnostic categories — all with a frequency apparently greater than that expected in a normal population. These mental diagnoses are familial imbecility and moronism, undifferentiated imbecility and idiocy and cranial anomalies.

Analysis of the methods used in surveying this large group showed that mass x-ray examination revealed only 7 cases, the 4-lead electrocardiographic method only 23, and combined x-ray and electrocardiographic study only 28 of the total of 49 cases of cardiovascular disease. Auscultation was necessary for detection in 14, and sphygmomanometry in 7 cases.

Although generally impractical for large surveys, it was concluded that determination by all four methods was necessary for accuracy.

We are indebted to Dr. Norman Pursley, director of the Gracewood Training School, who placed the facilities of his institution at our disposal, Dr. Theo Thevaos, pediatrician, who helped in the initial survey of the patients, Dr. Harry B. O'Rear, professor of pediatrics, Medical College of Georgia, who re-examined all patients with congenital heart disease for associated anomalies, and Mrs. Betty Beall, technician, who obtained over 1000 electrocardiograms during this study.

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FURTHER OBSERVATIONS CONCERNING THE SALIVARY TRANSPORT OF IODIDE*

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RECENTLY Thode, Jaimet and Kirkwood,[1] of Hamilton, Ontario, reported excellent correlation between thyroidal status and the ratios obtained when the concentration of I^{131} in mixed saliva (that is, serous and mucous) was related to either total or protein-bound radioactivity in the plasma twenty-four hours after administration of the tracer. Ratios in hyperthyroid patients were markedly lower and in myxedematous patients markedly higher than those found in normal subjects.§ It was suggested that the saliva test might "provide additional information con-

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§The range of activity ratios reported by Thode, Jaimet and Kirkwood[1] was as follows:

Saliva I^{131} to Plasma I^{131}	—	hyperthyroid patients, 0.22-26.9
		euthyroid subjects, 16.5-45.4
		hypothyroid patients, 28.8-161.6
Saliva I^{131} to PBI^{131}	—	hyperthyroid patients, 0.25-40.0
		euthyroid subjects, 160-235
		hypothyroid patients, 338-3200.

cerning thyroid-salivary function as well as an excellent diagnostic test."

In a previous publication[2] we reported that ratios of salivary I^{131} to plasma I^{131} of 7 to 30 could be obtained after stimulation of salivary flow by the chewing of paraffin. The absolute magnitude of saliva/plasma (S/P) gradients for inorganic iodide was not significantly correlated with thyroid status, although 3 of the myxedematous subjects demonstrated diminished salivary osmotic performance in their capacity to concentrate iodide and to withhold chloride.

The apparent contradiction between these results merits explanation. The discrepancies cannot be attributed to differences in methods of radioactive assay. However, the two studies differed significantly in the manner in which salivary specimens were obtained and the intervals between administration of I^{131} and collection of saliva. In our studies chewing of paraffin was employed as a standardized stimulus to salivary flow. Moreover, samples were collected within a few hours of the administration of radioiodide in order that plasma radioactivity might consist entirely of inorganic I^{131}. Since, as was demonstrated chromatographically, salivary radioiodine was also entirely inorganic, the S/P ratios reported were indicative of the iodide-concentrating capacities of stimulated salivary glands. On the other hand, Thode, Jaimet and Kirkwood[1] collected saliva without stimulation twenty-four hours after the oral administration of I^{131}. By relating salivary radioactivity to total or protein-bound radioactivity in the plasma, they obtained a striking inverse correlation between S/P ratios and thyroid activity. The precise physiologic significance of their ratios warrants examination.

It is well known that in myxedematous patients, there is very little replacement of inorganic radioactivity of the plasma by protein-bound radioactivity within twenty-four hours of the administration of inorganic I^{131}; in thyrotoxic patients replacement is almost complete.[3,4] The differences are due to the relative rapidity with which the thyroid gland removes inorganic radioiodide from the circulation and reintroduces the radioactivity into the blood stream in the form of labeled hormone. Thus, at twenty-four hours the circulating radioactivity is low in myxedema and predominantly inorganic in nature, whereas circulating I^{131} is high in thyrotoxicosis and is principally protein bound.[3,4] If salivary glands were pervious only to inorganic iodide, one might anticipate that the hyperthyroid subjects would have little radioactivity available for salivary elaboration whereas the reverse would obtain in myxedema. Furthermore, since the salivary glands concentrate inorganic iodide, the differences in the partition of plasma radioactivity might be exaggerated more than could be surmised from the conventional conversion ratios:

$$\text{plasma } \frac{\text{Protein Bound } I^{131}}{\text{Total } I^{131}}$$

In such circumstances, the close correlation reported by Thode, Jaimet and Kirkwood[1] between thyroid status and S/P ratios (especially saliva I^{131} to PBI^{131}) would not be surprising. However, the procedure that they have proposed would chiefly reflect variations in the partition of plasma radioactivity rather than intrinsic differences in salivary function.

To test this hypothesis, experiments were performed in subjects with diverse states of thyroidal and hypophyseal activity (Table 1). An attempt was made to simulate the pattern of plasma radioactivity that characterizes the thyrotoxic patient twenty-four hours after the administration of inorganic I^{131}. Nine subjects were given intravenous injections of 50 microcuries of I^{131}-labeled l-thyroxine* containing 1 to 4 microgm. of iodine. On the following day, samples of plasma and mixed saliva were collected and assayed for radioactivity† exactly as described by Thode, Jaimet and Kirkwood.[1] In addition, specimens of saliva were obtained after stimulation by chewing of paraffin.[2] In all subjects, plasma radioactivity was 92 to 99 per cent precipitable by trichloracetic acid. When ratios were derived by relating salivary radioactivity to either the total or protein-bound radioactivity in plasma, these ratios were less than 1.27 in every instance; in only 1 subject did they exceed 0.80 (Table 2). All ratios, regardless of the thyroid status of the experimental subject, fell within the extreme hyperthyroid range as described by the Ontario group. The results indicate that the S/P ratios reported by Thode, Jaimet and Kirkwood[1] are principally determined by the partition of plasma radioactivity into organic and inorganic moities rather than some independent "thyroid-salivary function."

From the data of Thode, Jaimet and Kirkwood[1] saliva/plasma ratios for inorganic I^{131} were calculated:

$$\text{S/P-inorganic } I^{131} = \frac{\text{S/P-total } I^{131}}{\text{1-conversion ratio}}$$

These were found to average 38.1 in euthyroid, 31.1 in hyperthyroid and 74.2 in hypothyroid patients. Only the hypothyroid values differed significantly from the other groups. Inorganic ratios were somewhat greater than those that we had reported. The discrepancy may have resulted from variation in the technic of salivary collection. Others have suggested that the elaboration of iodide in mixed saliva can be altered by the rate of salivary flow,[5] by the proportion of serous secretion[6] and by the nature of the stimulus to salivation.[6] In each of the 9 patients noted above, salivary flow was less rapid and S/P ratios were greater in the unstimulated salivas than in the specimens collected with paraffin stimulation (Table 2). It is of interest to inquire whether the significantly greater ratios for S/P-inorganic I^{131} calculated in the hypothyroid patients of the Ontario group may not reflect a disproportionate sluggishness

*Available from Abbott Laboratories, North Chicago, Illinois.

†Liquid specimens were counted in a well-type scintillation counter. A minimum of 10,000 counts above background were obtained for each sample of saliva, plasma and redissolved trichloracetic acid precipitate of the plasma.

in the unstimulated salivary flow of the myxedematous patient.

To explain the high ratios that they observed in hypothyroidism, Thode, Jaimet and Kirkwood[1] postulated an increased activity within the salivary glands of an enzymatic iodinating-deiodinating system ("tyrosine iodinase"). This view must be projected against certain physiologic factors that would limit the magnitude of S/P gradients regardless of the efficiency of any salivary process. The first of these rate-limiting phenomena is salivary blood flow. Thus, if protein-bound radioactivity were the sole or the principal source of radioactivity appearing in the saliva, a saliva to plasma PBI^{131} ratio of 3200, as noted by these authors, would necessitate deiodination during the collection period of an amount of thyroxine equivalent to that contained in 3 liters of plasma. Furthermore, since thyroxine is excluded from the erythrocyte,[4] a total salivary blood flow roughly equivalent to a minute's cardiac output — that is, about 6 liters — would have been required during the collection period.

Secondly, even if salivary deiodination of thyroxine or its breakdown products were instantaneous, this process could not exceed the rate of turnover of thyroxine in the body as a whole. In man, including patients with myxedema, thyroxine is distributed in approximately 10 liters of body fluid, and is metabolized at the rate of approximately 10 per cent per day.[7,8] Calculation reveals that about 0.6 cc. per minute is the total body clearance of thyroxine. It follows that saliva to plasma PBI^{131} ratios greater than 0.6 could not be obtained at a salivary flow of 1 cc. per minute even if the salivary glands were the sole site for the degradation of thyroxine or its metabolites.

TABLE 1. *Clinical Status of Experimental Subjects.*

SUBJECT	DIAGNOSIS*	24-HR. UPTAKE OF I^{131} BY THYROID GLAND†	PBI^{127}
			microgm./100 cc.
D.N.	Nontoxic goiter	50	5.6
B.D.	Acromegaly	22	3.6
D.R.	Primary myxedema	1	5.4
E.C.	Primary myxedema	3	1.1
E.D.	Pituitary myxedema	26	2.6
S.K.	Surgical myxedema	2	0.6
D.H.	Thyrotoxicosis	84	12.5
M.T.	Thyrotoxicosis	91	9.2
S.W.	Thyrotoxicosis	80	3.2

*D.R. was being maintained on 0.12 gm. of desiccated thyroid per day, & S.W. was receiving 300 mg. of propylthiouracil per day; both euthyroid clinically at time of studies (all other subjects untreated).

†Twenty-four hr. after oral administration of 10 microcuries of carrier-free inorganic I^{131} percentile accumulation of radioactivity within thyroid gland measured with directional scintillation counter containing thallium-activated sodium iodide crystal.

The foregoing considerations do not preclude an important physiologic role for salivary "tyrosine iodinase."[1,9] It seems clear, however, that variations in ratios of salivary I^{131} to the total or protein-bound I^{131} of the plasma, as described by Thode, Jaimet and Kirkwood,[1] although correlating well with thyroid status, depend more on differences in the rate of replacement of the plasma's inorganic by protein-bound radioactivity than on inherent differences in the function of the salivary gland. Experimental data and theoretical considerations have been presented to support this view.

TABLE 2. *Salivary Gradients after Administration of I^{131}-Labeled l-Thyroxine.**

SUBJECT	STIMULATED SALIVA†			NONSTIMULATED SALIVA‡		
	FLOW	S/P-TO-TAL I^{131}§	S/P-PBI^{131}§	FLOW	S/P-TO-TAL I^{131}	S/P-PBI^{131}
	cc./min.			*cc./min.*		
D.N.	2.26	0.16	0.16	0.67	0.38	0.38
B.D.	5.60	0.19	0.20	1.86	0.46	0.49
D.R.	0.86	0.38	0.39	0.51	0.80	0.81
E.C.	0.76	0.81	0.82	0.71	1.26	1.27
E.D.	1.04	0.21	0.23	0.47	0.70	0.75
S.K.	3.56	0.22	0.22	1.17	0.52	0.52
D.H.	1.84	0.16	0.16	0.76	0.53	0.55
M.T.	3.46	0.06	0.06	1.90	0.07	0.08
S.W.	2.58	0.03	0.03	1.33	0.14	0.14

*Subjects given intravenous injections of 50 microcuries of I^{131}-labeled l-thyroxine containing 1 to 4 microgm. of iodine. Salivary studies performed 24 hr. later.

†"Stimulated saliva": mixed saliva (serous & mucous) collected by continuous expectoration into beaker during 5 min. of chewing paraffin pledget. This had been preceded by 5 min. of chewing another paraffin pledget & by 2 min. of rinsing mouth with tap water.

‡"Nonstimulated saliva": mixed saliva collected by direct expectoration into beaker without preliminary or concomitant chewing of paraffin. In D.N., D.R., E.C. and M.T. "stimulated salivas" obtained first, and "nonstimulated salivas" collected after 15-min. interval. Salivary specimens obtained in reverse sequence in subjects B.D., E.D., S.K., D.H. & S.W.

§Ratio of radioactivity in 3 cc. of saliva (S), and 3 cc. of untreated plasma (P-total I^{131}) or 3 cc. of plasma precipitated with trichloracetic acid, washed & redissolved to original volume with sodium hydroxide (P-PBI^{131}).

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OCCURRENCE OF THE "L.E." PHENOMENON IN A PATIENT WITH A SEVERE PENICILLIN REACTION

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THE diagnosis of systemic lupus erythematosus has been greatly facilitated by the discovery of the L. E. cell.[1] Several reports have appeared in the literature emphasizing the specificity of the test.[2-5] Dubois[6] stated that in over 1000 tests performed, a false-positive reaction had yet to be encountered and that, in his experience, this test is pathognomonic if positive. Walsh and Egan[7] also commented on the reliability of this test in the diagnosis of disseminated lupus, but later Walsh and Zimmerman[8] reported the finding of L. E. cells in concentrated bone-marrow preparations from 3 patients with severe penicillin reactions. Haserick,[9] in reviewing the L. E. cells described by Walsh and Zimmerman, agreed that they undoubtedly represented the L. E. phenomenon, but he noted that these preparations were "low-grade positive." He emphasized the relation between the number of L. E. cells present and the degree of positivity of the test, and further stated that he had never observed a false-positive reaction in the +++ and ++++ group. In view of the occurrence of L. E. cells in severe penicillin reactions, the suggestion was made that the L. E. phenomenon might be related to the state of hypersensitivity.[8] Isolated reports have also appeared on the finding of L. E. cells in patients with hemolytic anemia,[3] miliary tuberculosis,[3] pernicious anemia in relapse,[10] dermatitis herpetiformis,[10] chronic discoid lupus,[10] leukemia,[10] generalized moniliasis[11] and multiple myeloma.[12] Of interest is the recent report by Perry and Schroeder[13] of the appearance of a syndrome simulating lupus erythematosus disseminatus in hypertensive patients receiving hydralazine therapy. These findings have since been confirmed by others.[14]

CASE REPORT

R.P. (V.A.H. 22679), a 64-year-old man of Italian extraction, was admitted to the hospital on February 11, 1954, with the chief complaint of dyspnea, hemoptysis and asthenia. The diagnoses of chronic bronchitis, pulmonary emphysema, pulmonary fibrosis, bronchiectasis, cor pulmonale, hypertensive and arteriosclerotic heart disease and diabetes mellitus had been established in the past. On a previous admission to this hospital, a mild reaction characterized by a generalized pruritus had followed the use of Neo-penil. The present illness had begun several weeks before admission, when he noted recurrent shortness of breath on exertion, intermittent hemoptysis, a more distressing cough, weakness and general malaise. On the day of admission he was found lying in bed dyspneic and cyanotic, and was referred by his family physician to the hospital for further treatment.

Physical examination revealed a well developed and fairly well nourished man lying in bed, very dyspneic and presenting definite cyanosis of the skin, lips and mucous membranes. The cervical veins were moderately distended. The chest was emphysematous. Crepitant rales were present in the lower third of the lung fields posteriorly. Examination of the heart showed a left border extending to the anterior axillary line, an increased pulmonic 2d sound and a gallop rhythm. Other significant findings included a slightly enlarged and tender liver, whose edge extended 5 cm. below the right costal margin, and ++ clubbing of the fingers and toes.

The temperature was 102°F., the pulse 122, and the respirations 38. The blood pressure was 200/105.

Examination of the blood disclosed a red-cell count of 6,100,000, with a hemoglobin of 19.1 gm. per 100 cc. and a hematocrit of 60 per cent, and a white-cell count of 15,000, with 75 per cent neutrophils, 8 per cent stab forms, 10 per cent lymphocytes and 7 per cent monocytes. The platelets numbered 160,000; the reticulocyte count was 2 per cent, and the fragility test was negative, as was the blood Kahn test for syphilis. The urine had a specific gravity of 1.020 and gave a + test for albumin; the sediment contained an occasional white cell per high-power field, with no red cells or casts. Urobilinogen was present in the urine in a 1:10 dilution. The blood urea nitrogen was 34 mg., and the fasting blood sugar 215 mg. per 100 cc. The serum electrolytes were normal. The total protein was 8.2 gm. per 100 cc., with an albumin of 5.3 and a globulin of 2.9 gm. per 100 cc. Liver-function tests were negative, including the serum bilirubin, which was 0.4 mg. per 100 cc. Examination of the peripheral blood for L. E. cells was positive (Fig. 1). An electrocardiogram was consistent with cor pulmonale. A roentgenogram of the chest demonstrated generalized cardiac enlargement, pulmonary congestion and possibly bronchopneumonia.

The diagnoses were pneumonitis and congestive heart failure. Treatment consisted of digitalis, mercurial diuretics, phlebotomies, penicillin and streptomycin. Penicillin was given for a 12-day period and streptomycin for 10 days. Added to the treatment, at a later date, were expectorants, steam inhalations and Raudixin. The patient made a satisfactory recovery and was discharged on February 26, only to return 36 hours later complaining of a severe skin rash, pruritus and dysphagia. On examination, a generalized urticarial reaction was noted. Shortly afterward, a temperature of 101.2°F. and arthralgias of the knees, ankles, shoulders and left wrist developed. The peripheral blood was examined and found to contain L. E. cells (low-grade positive). Because of the severe pruritus and dysphagia, 20 mg. of ACTH in 1000 cc. of physiologic saline solution was given intravenously, only to be discontinued after 2 days. By this time the fever, arthralgias and the dysphagia had subsided, but the patient became disoriented. Within 3 days of discontinuance of ACTH his mental status cleared, and he was discharged shortly thereafter. Although repeated preparations were examined, no L. E. cells were found. One month later, when he returned for a follow-up study, it was ascertained that he was feeling well. Again, several preparations failed to reveal the presence of the L. E. phenomenon.

DISCUSSION

The L. E. cell may be defined as a leukocyte, usually a polymorphonuclear cell, containing a large, round, homogeneous inclusion body consisting of partially depolymerized desoxyribonucleic acid. This inclusion body is derived from nuclear substance of either lymphocytes or neutrophils and is phagocytized by normal polymorphonuclear cells, producing the L. E. cell. The factor responsible for the production of the phenomenon has been shown to reside in the gamma-globulin fraction of the serum and antigenically is quite distinct from any fraction in normal gamma globulin.[16] The significance of a positive

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L.E. test in patients with severe penicillin reactions has been amply described by Walsh and Zimmerman,[8] who stated that it may have one of a number of implications: that coincidental lupus erythematosus is present; that the test is nonspecific; that penicillin reactions may produce pathologic and serologic changes related to systemic lupus erythematosus; and that the L. E. phenomenon may be related to hypersensitivity without the histologic changes of systemic lupus. Evidence for the last hypothesis is now accumulating. Finch[17] has produced lupuslike cells by the in vitro incubation of normal human granulocytes in rabbit antiserum developed against these cells. Zimmerman et al.[18] have been able to cause nucleophagocytosis by the production of rabbit antileukocytic serum. It was their opinion that nucleophagocytosis resulted from leukocytic sensitization and that a similar mechanism was responsible for the L. E. phenomenon. Similar changes have been produced by the addition of antispleen, antithymic or antinuclear antiserum to plasma rich in leukocytes.[19]

That this patient had disseminated lupus erythematosus is highly improbable. It seems more likely that the occurrence of the L. E. phenomenon in patients with severe penicillin reactions is on the basis of an immunologic mechanism.

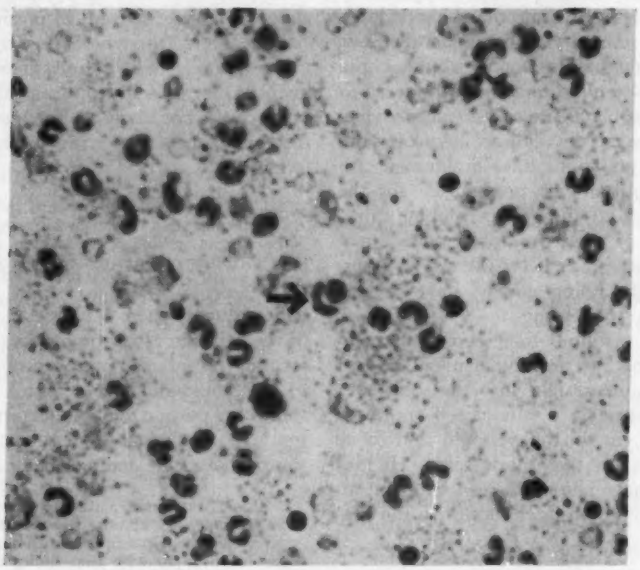

FIGURE 1. *Weakly Positive L.E. Preparation in a Patient with a Severe Penicillin Reaction (X180).*

SUMMARY

The occurrence of the L. E. phenomenon in a patient with a severe penicillin reaction is reported. Although no definite conclusions can be made, it seems highly probable that an immunologic mechanism is responsible for the L.E. phenomenon.

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SPECIAL ARTICLE

THE DECISION TO STUDY MEDICINE

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FROM the time that he prepares his application for medical school to the time that he sits down to write his memoirs the physician frequently finds himself confronted with the question of why he chose to become a doctor. Often his answer is considered to indicate the chances of his future success in medicine or the degree of his present devotion to the profession. Experts in vocational guidance have designated certain attitudes and aptitudes as prerequisite for the prospective physician, and the general public entertains its own notions of what prompts a young man to study medicine; but it may be of interest to ascertain what certain outstanding doctors have said in their autobiographies concerning the circumstances and motivations that surround their choice of medicine as a career. More than most other men, the doctor is enabled to acquire insight into the sources of human action, and, through a candid self-appraisal, he may shed much light on the personal and social forces that lead one to the study of medicine. He may also help to clarify the relation between youthful attitudes toward medicine and later success in the profession.

VOCATION

A study of medical autobiographies shows that many doctors are convinced that they entered their profession because of a special calling. Some of these doctors explain this calling on the basis of a desire to benefit humanity. Thus, Girolamo Cardano,[1] the sixteenth-century author of the first full-dress medical autobiography, states that he shunned the riches and ready advancement that would have followed his entrance into the family law firm so that he could pursue the more useful occupation of caring for life itself as a doctor.

The autobiography of Albert Schweitzer, however, presents in a tone of modest simplicity an unequivocal account of the power of humanitarian ideals to inspire one to undertake the study of medicine. Schweitzer, as a schoolboy in his native Alsace, was pained by the sight of the wretched home surroundings of some of his schoolfellows and was constantly comparing his own happy life with the care and suffering that filled the lives of others. Finally, at the age of twenty-one, he resolved not to accept his happiness as a matter of course but to give something in return for it. He decided to continue to live for his musical and theological studies until he reached the age of thirty and to devote himself completely from that time forward to the direct service of humanity. His search for a career in which he could most practically and effectively help his fellow man ended when he read about the need for medical missionaries in Equatorial Africa. Here, thought Schweitzer, was a profession more valuable than merely preaching the religion of love because it meant putting this religion into actual practice. Accordingly, at the age of thirty he entered medical school. Referring to this time, he writes as follows:

> I did, in truth, look forward to the next few years with dread. But the reasons which determined me to follow the way of service I had chosen, as a doctor, weighed so heavily that other considerations were as dust in the balance.[2]

Sometimes when a physician attributes his choice of medicine to altruistic motives a more rigorous self-scrutiny reveals the presence of certain qualifications to his noble-minded idealism. An example is the following portion of a letter written by James Hinton,[3] the eminent English aural surgeon, in 1841, shortly before he entered medical school:

> I feel sometimes a deeper desire than I can express to be in some way or other the benefactor of my species, and yet I cannot help suspecting that pride and ambition have far more to do with that desire than philanthropy. I do not find in myself the same willingness to be useful in a way of unnoticed — perhaps despised — toil as I do in ones that should procure me respect and esteem, and be gratifying to vanity.

Many physicians who claim that they were impelled to study medicine because of a special calling do not explain this calling on altruistic grounds but instead refer to an inexplicable desire to become doctors, which they had from their earliest days. Samuel D. Gross,[4] the famous professor of surgery at Jefferson Medical College from 1856 to 1882 and the organizer of the American Surgical Association, makes the following statement in his autobiography:

> I had from my earliest childhood the strongest desire to be a "doctor." How that feeling was engendered I have never been able to explain . . . There are natural-born poets; and, if there ever was a natural-born doctor, I was that one.

John M. T. Finney,[5] the American specialist in visceral surgery who introduced the operation of gastroduodenostomy, states that the study of medicine was "the one thing and the one thing only" that he ever had in mind as his life's work. He expresses pity for his less fortunate friends who were forced to make a decision concerning their future careers.

In Arthur E. Hertzler's[6] homespun autobiography, *The Horse and Buggy Doctor*, the famous Midwestern surgeon says that he has no idea why he chose to study medicine but that he "never gave a thought to doing anything else than doctoring folks." With his typical

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earthly frankness Hertzler goes on to deride the sanctimonious airs of some of his colleagues:

> Doctors of medicine also occasionally profess altruistic motives, but I never knew one who amounted to anything making any such pretensions. These gentlemen talk much of their "noble calling." Any calling is noble in exactly the proportion that nobility is brought to it, as for instance carpentering. Most people who amount to anything start and go at high speed wherever they find themselves.[6]

Interest in Science

Although many doctors, such as those mentioned above, believed that a special calling drew them into the medical profession, the majority testify in their autobiographies to the lack of any particular vocation for a career in medicine. A basic interest in general science lay behind the choice of many in this group. This primary love of science led some of them to devote their lives to medical research and teaching rather than to medical practice. Walter B. Cannon, the physiologist, resolved definitely to go to medical school only after he had become deeply interested in his courses in chemistry and biology at Harvard College.[7] The famous medical historian Henry E. Sigerist, as a student of science at the University of Zurich, could not bear to specialize in a small facet of science like chemistry or zoology or botany and consequently chose the study of medicine, which he believed would provide him with the broadest view of science and human life.[8]

A factor of outstanding importance in calling the attention of young men to science in the latter part of the last century was the interest aroused by Darwin's theories of evolution and the passionate controversy excited by them. Walter B. Cannon recalls how avidly he followed Huxley's debates on evolution with Gladstone and how eagerly he read the controversial books and articles on scientific topics that were being publicized at the time. "This serious reading," says Cannon,[7] "strongly influenced me in coming to the decision to try to obtain a college education." Likewise, Sigmund Freud recounts his early fascination with Darwinism, which, he says, inspired him as an extraordinary advance in the understanding of the world and greatly influenced him to become a medical student.[9] Harvey Cushing's monumental biography of Sir William Osler pictures the young Osler at Trinity College in Toronto ostensibly preparing to enter the ministry but actually becoming more and more absorbed in collecting natural specimens and examining them under a microscope. Strangely enough, the good clergymen who were Osler's teachers encouraged his scientific activities and, in accordance with the spirit of the times, were themselves inclined to dabble in science:

> Ministers with an interest in the natural sciences, particularly in those days when Wilberforce and Huxley represented the antipodes of thought . . . made dangerous teachers for youths whom they expected to induct into the Church. To them science was a pastime; but the pleasant avocation of one generation easily becomes the vocation of the next . . . Another environment, an earlier decade, would almost certainly have seen him enter the Church.[10]

Influence of Others

Among doctors who discount all claims for a special calling for medicine many ascribe their choice of a career to the direct influence of a particular person. The father very often plays a leading role in determining the future career of his son. Karl L. Schleich, who introduced infiltration anesthesia in 1894, reveals in his autobiography how powerful an influence a domineering father can have on his children, especially, perhaps, when he is himself a noted German physician.

> I was entirely under the spell of my honored and venerated father — a compulsion from which I could never free myself as long as I lived . . . Medicine to me, was the inevitable tribute of love.[11]

Paternal influence may be more subtle, as with Sir Benjamin Brodie, one of the pioneers in surgery, who speaks of his father's relation with himself and his brothers in the following way: "We supposed that he left us to choose our professions for ourselves, but the fact was, as I now believe, that without our being aware of it, he himself directed our inclinations."[12] Brodie goes on to say that he had no taste for the profession into which his father guided him but that he was like many other medical students who "feel their new pursuit to be unattractive enough in the beginning; but as they go on, and acquire knowledge, and find that they obtain some degree of credit, the case is altered; and from that time, they become every day more interested in what they are about."[13]

The aspirations of a domineering mother may determine her son's career, especially when her ambitions for her children are inflamed by her disappointment with a ne'er-do-well husband. This situation is illustrated in the early home life of Sir Arthur Conan Doyle,[14] the physician who created the character of Sherlock Holmes.

The desire of the scion of a well established medical family to inherit the family's good name and fortune, as well as to fulfill his duty in maintaining the family traditions, is expressed in the autobiography of Jean Antoine Chaptal,[15] the physician and politician of Napoleonic France who gave nitrogen its name.

The great British surgeon John Hunter[16] was undoubtedly influenced in his choice of a career by the example of his two elder brothers, who had studied medicine.

That the influence of a friend or an acquaintance may turn one's interest toward medicine is attested by Gordon S. Seagrave,[17] who recalls how he was completely captivated, at the age of five, by a medical missionary, — a big, friendly Irishman, — whom he firmly resolved to emulate.

A teacher may influence a pupil to study medicine either through the powerful inspiration of his personality, which awakens a love for medical science in his

students, or through the less dramatic medium of kindly counsel. Paul Ehrlich, whose eyes were opened to the beauties of medicine by his revered master, Wilhelm Waldeyer,[18] is a product of the former type of influence, and an example of the latter is Hans Zinsser, whose teachers gave him the advice to study medicine because they believed he needed the mental discipline of a medical education before embarking on a career as a bacteriologist.[19]

Frequently, a child undergoing treatment for an illness is so allured by the doctor's personality or by the nature of his work that he resolves then to make medicine his career, or at least retains so favorable an image of the medical man and the practice of medicine that he acknowledges in his autobiography the crucial influence that this early experience may subconsciously have exerted on the choice of his profession. Because of the family doctor's role as wise friend and counselor, he is sometimes directly asked for advice concerning a young man's choice of career — a practice that often produces another recruit for medicine. Wilfred T. Grenfell[20] states that his family physician, in describing the attractions of medical science, had only to show the young Grenfell a pickled human brain to stimulate in him a keen desire to study medicine.

Medicine As a Last Resort

Many physicians who do not attribute the choice of their profession to the influence of any particular person describe their decision as a process of eliminating other attractive but unpromising possibilities until medicine was left as the only choice. Sir Robert Christison, who became professor of materia medica at the University of Edinburgh, wanted to study engineering, but his father thought poorly of the opportunities in this profession, and young Robert had to settle for a medical career. Soon afterwards, however, engineers became very much in demand, and the noted authority on toxicology asks somewhat wistfully in his autobiography, "What if I had stood out for engineering?"[21] J. Marion Sims, who revolutionized gynecologic surgery a hundred years ago with his operation for vesicovaginal fistula, describes very clearly the process by which he chose medicine:

> A graduate of a college had either to become a lawyer, go into the church, or to be a doctor. I would not be a lawyer; I could not be a minister; and there was nothing left for me to do but to be a doctor — to study medicine or to disgrace my family. . . .[22]

Sims goes on to say that he would have preferred to go into business, but such an occupation was considered degrading for a man with a college education. Charles Caldwell, the founder of two medical schools in the West, chose medicine only after his father had condemned his predilection for the law and the rest of his family had persuaded him to relinquish his subsequent plans for a military career.[23]

Some men in their autobiographies frankly admit that their choice of medicine was based on the prestige or the lucrativeness of the profession. Sir Joseph Fayrer, who later made important studies in tropical medicine, witnessed, at the age of nineteen, a severe epidemic of yellow fever in Bermuda, where his father was stationed as a naval officer. During this crisis he was so strongly impressed by the exalted social position of the medical officers that he resolved to become a doctor. "The youngest of them," says Fayrer, "at that time seemed of more importance than an admiral or a general."[24] In an engaging autobiography Wenzel Krimer, a German military surgeon during the Napoleonic Wars, relates how, as a young signboard painter, he was employed by the municipal physician, who, he soon decided, was an ignoramus. If this fool was able to live in such luxury, reasoned Krimer, he, himself, could do at least as well in the same profession. Forthwith he became a medical apprentice.[25]

The desire to attain indirectly other goals by becoming a doctor is encountered in several medical autobiographies. Ronald Ross, who proved that mosquitoes transmit malaria, acquiesced in his father's insistence that he study medicine because, by joining the Medical Service, he could be stationed in India, where he dreamed of leading a leisurely life with shooting and riding and any other hobbies he might have a mind for:

> But I had no predilection at all for medicine and, like most youths, felt disposed to look down upon it . . . Consequently on 1 October 1874 my father himself delivered me at the Hospital . . . I was not happy that day.[26]

The well known professor of surgery at Columbia, Arpad Gerster,[27] says that he chose medicine to become a ship's doctor and thus to live a life of romance and adventure and indulge his taste for natural science.

Some authors of medical autobiographies describe how they drifted into medicine only after attempting other occupations. Oliver Wendell Holmes tried law school and writing for a periodical before he gave them up and entered medical school. Literature, however, really remained his truest love.[28] Victor Heiser,[29] the author of *An American Doctor's Odyssey*, tried his hand at many jobs and even spent a year in engineering school before he decided to study medicine. The great exponent of the climatic treatment of tuberculosis, Edward L. Trudeau, makes the following remarks in his autobiography:

> . . . I was trying to get some occupation and settle on some career. I studied for three months in the School of Mines, took a position for a while in a broker's office, and tried various other occupations spasmodically, but soon gave them up, as I was a failure at everything I undertook.[30]

Impulse

Sheer impulse seems to be the only explanation for the choice of medicine on the part of some doctors who disclaim any specific calling for their profession.

Havelock Ellis states that he never felt the faintest vocation for any course of life, and the question of his future career remained for several years a puzzling and painful problem, to which he could see no solution. Then he describes the following experience, which occurred after he began to read the *Life and Letters of James Hinton:*

> Suddenly I leapt to my feet as though I had been shot. "I will become a doctor!" a voice within me seemed to say . . . in settling the greatest practical question of life, I settled it in an instant, without even any deliberation at all — for the idea of becoming a doctor had never before so much as entered my head — and settled it so finally that I never once called my decision in question.[31]

Edward Trudeau also invokes a mysterious, sudden impulse to explain his choice of medicine. He states that he felt the need to find some work to escape his careless, drifting life and goes on as follows:

> I knew no doctors or anyone connected with a medical college, but I often did things purely on impulse, which came to me as a sort of auto-suggestion. . . . So little faith did my friends at the Club have in my doing any work at all that I remember when my decision to study medicine was announced to a group of men in the Club, Mr. Dan Moran said, "I bet five hundred dollars he never graduates," and no one was found to take the bet![32]

Despite Trudeau's testimony one may speculate on the subtle influence that the knowledge of his medical ancestry and the experience of nursing his tuberculous brother may have had on his decision.

Indeed, the mysterious forces invoked by some doctors in explaining their choice of occupation occasionally become frankly supernatural. Thus, Johann Dietz,[33] a barber surgeon in the Prussian army of the late seventeenth century, writes that, when his father told him he must decide immediately how he would earn his living, he dreamed all night of medicine and was confident the next day that God had revealed to him in his sleep the path that he should follow. Benjamin Rush hesitated before deciding on medicine because of a predilection for the law, and, even after embarking on his medical career, he experienced periods of regret when he was tempted to abandon medicine and prepare himself for the law: "But providence overruled my intentions . . . . I have seen the hand of heaven clearly in it."[34]

Women in Medicine

Turning to the autobiographies of women physicians one finds many examples of the crusading spirit and the conscious sense of dedication to a righteous cause. Epecially is this true of the early pioneers, who persevered in acquiring a medical education and establishing themselves as doctors despite tremendous obstacles. The character of many of these courageous women is exemplified by Elizabeth Blackwell, who in 1849 was the first woman in America to receive a medical degree. Her desire to become a doctor arose from her recognizing the need for women physicians and the importance of disciplining her mind and body to perform constructive work instead of wasting her energies in the ordinary course of courtship and marriage. One gets deep insight into her personality on reading her description of how she reacted when the physicians whom she consulted for advice dismissed her ambition as impossible to achieve:

> This verdict, however, no matter from how great an authority, was rather an encouragement than otherwise to a young and active person who needed an absorbing occupation. . . . The idea of winning a doctor's degree gradually assumed the aspect of a great moral struggle, and the moral fight possessed immense attraction for me. . . .[35]

Marie Zakrzewska, who with Elizabeth Blackwell founded the New York Infirmary for Women and Children, the first hospital conducted wholly by women, showed extraordinary capacities and interests when still a young girl. At the age of ten Marie had to spend some time in a Berlin hospital as a patient. There she befriended one of the staff physicians, who not only let her accompany him on his ward rounds but even acquiesced in her plea for permission to visit the autopsy room. She spent her following vacation from school reading two huge tomes on midwifery and surgery. They so captivated her attention that while reading them she even forgot to attend autopsies![36]

However, the next generation of women physicians began to enter their profession in a more natural manner although the opposition to women in medicine was by no means completely dispelled. Elizabeth Cushier, who became the leading woman surgeon in America at the end of the last century, is a representative figure of this transitional period. Women doctors were accepted by the more progressive elements in the society, and, after Elizabeth Cushier spoke to her "advanced friends," as she calls them, of her inclination to study medicine, she was warmly encouraged by their enthusiastic approval of her plans.[37]

The autobiographies of women who have studied medicine since Elizabeth Cushier's time reveal, in most cases, roughly the same motivations governing their choice of occupation as those professed by the men. Alice Hamilton, noted for her studies of industrial hazards, describes, in the following passage, her outlook at the time when she and her sister decided to find some occupation to bolster their family's diminishing finances:

> There seemed only a few careers open to us — teaching, nursing, the practice of medicine . . . I chose medicine, not because I was scientifically-minded, for I was deeply ignorant of science. I chose it because as a doctor I could go anywhere I pleased — to far-off lands or to city slums — and be quite sure that I could be of use anywhere. I should meet all sorts and conditions of men, I should not be tied down to a school or a college as a teacher is, or have to work under a superior, as a nurse must do.[38]

S. Josephine Baker, prominent in children's welfare movements in New York, speaks candidly in her autobiography, as follows:

> I wish I could remember what made me choose medicine as a way of earning my living — for that is the conscious commercial attitude I had toward it at that time. I expect that even then I did not know my motive very clearly.[39]

But, like many other women in medicine, she shared the tough fiber of Elizabeth Blackwell, and opposition to her plans, far from acting as a deterrent, actually stimulated her to greater efforts on their behalf:

> . . . when I encountered only argument and disapproval, my native stubbornness made me decide to study medicine at all costs and in spite of everyone. . . . I am thoroughly convinced that obstacles to be overcome and disapproval to be lived down are strong motive forces.[39]

Humanitarian zeal, however, is by no means absent among the drives that motivated women of the later generations to study medicine. Rosalie Slaughter Morton, who saw active service on the fighting fronts during World War I, eloquently testifies to this fact:

> From the first day that I thought seriously about studying medicine, I held the profession in the highest idealism. To sign over one's life to the dedication of human needs: there could be no finer life to live! And so, inwardly ablaze with this desire, I met the opposition of my family.[40]

Conclusions

To judge, therefore, from the evidence of medical autobiographies, relatively few physicians are driven from the very beginning by an altruistic desire to be healers. Even many of those who claim a special calling confess that they are unable to explain why medicine so powerfully attracted them; among physicians, men and women, who deny a special calling for their profession, the reasons given to account for their choice run from a basic interest in science to the direct intervention of heaven. No consistent relation seems to hold between youthful predilections and future success in medicine. The perusal of medical autobiographies, however, reveals the fact that doctors — even those who claim to have drifted into medicine by the merest chance — usually develop a deep and abiding love of medicine as their medical knowledge increases and as they come into contact with patients. The abilities that can be utilized in the broad field of medicine are so many and diverse that success and personal satisfaction in the profession can attend the careers of the talented despite the circumstances that initially led them to undertake these careers. In striking contrast to a doctor's vivid account of early lack of enthusiasm for medicine his subsequent description of his professional life may be fraught with instances of unsparing devotion to his patients and to his science; sometimes he may even recount, simply and unpretentiously, episodes of heroic self-sacrifice.

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MEDICAL PROGRESS

TUBERCULOSIS (Concluded)

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RESECTION

To proceed to a brief discussion of the now popular operation of resection, particularly segmental resection, one should speak first of the papers of Chamberlain et al.[57] and O'Brien et al.[58] presented at the meeting of the American Association for Thoracic Surgery in March, 1953. Of Chamberlain's 300 consecutive patients followed for one to five years 93.7 per cent were reported as living and well, 3.3 per cent living with disease, and 3 per cent dead. One must, of course, realize that these were minimal lesions with more than adequate drug coverage. The paper of O'Brien et al. is important because it pictures the present chaos in writing on resection therapy.

Many other reports of excellent though early post-resection results are available. For instance, the Veterans Administration Hospital in Madison, Wisconsin, reports[59] 353 resections with 7 deaths, 2 of which were charged to the anesthetic.

The dreaded complication of a bronchial fistula persisting after resection still occurs although improvements in chemotherapy may eliminate some of its dangers. Roll[60] describes ulceration of the bronchial stump in 24 per cent of 400 resections but does not specify the prevalence of fistulas. Murphy,[61] from the Veterans Administration Hospital in Oteen, North Carolina, reports bronchial fistulas in 15.3 per cent of 143 resections.

PLOMBAGE

Extrapleural plombage of different sorts has not stood the test of time, but extraperiosteal compression is now in favor. Woods and Buente[62] present 270 cases in which the material inserted into the extraperiosteal space consisted of lucite balls. The results to date are excellent, but there is a frequent persistence of positive sputum. Reports on the use of Fiberglas[63] are on the whole unsatisfactory. A polyvinyl plastic-sponge prosthesis for use after resection is a promising development.[64]

CHEMOTHERAPY

General Aspects

The point of greatest interest in the problem of tuberculosis today is that of the effect of drugs on tuberculous infection in man. At the start the extreme importance of the annual conferences (and the quarterly reports) of the Veterans Administration, Army and Navy, ably initiated, conducted and reported by Drs. John Barnwell and Arthur Walker and their host of collaborators, should be re-emphasized.

Before the comparative value of the different drugs and their combinations is discussed certain general statements should be made. One must stress the point that the drug treatment of a case of tuberculosis should not be entered into lightly because the original course of therapy is all important and, once started, should usually not be interrupted until the desired result has been reached. There is next the matter of dosage and the realization that one cannot treat on the basis that if a little drug is good a great deal is better, and also that whereas there now seems to be no advantage in giving more than small doses of isoniazid the same principle does not hold for all antituberculosis drugs. And in the long-term chemotherapy required in tuberculosis not one drug but a combination of drugs seems necessary if resistance is to be avoided. However, with isoniazid, even this supposedly established principle has been questioned by such competent observers as McDermott and Muschenheim.[65] The next question concerns daily versus intermittent (usually twice a week) dosage of drugs, particularly streptomycin. But, again, what is good with streptomycin is not necessarily good with other drugs, and even with streptomycin a preliminary course of daily injections for four to six weeks seems helpful in a few very seriously ill patients. The next matter is one of duration of treatment and the present trend toward long courses, usually of a year or even much more. A few die-hards even say that, once started, the drug should be continued indefinitely. The Veterans Administration has a very interesting statistical study underway to try to determine how long a period of chemotherapy is necessary after the "target point" has been reached. The "target point" is defined for this study as follows: negative cultures of sputum or gastric contents, at monthly intervals, for three months; no cavities in films or planigrams; and stationary x-ray appearance (or slight shrinkage) for three months. But, with the periods of chemotherapy being steadily increased, one begins to wonder what part is being left to the patient's own resistance, which must still play a part in the eventual healing. Then there is always the problem of the toxicity of each drug.

When the facts have been taken into account and a given patient has been treated for about six months one takes stock, paying particular attention to the

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possible persistence of cavities, which usually call for surgical treatment. If there is a cavity the sputum is usually positive, and in at least half the cases under streptomycin therapy the bacilli are resistant. But in some cases the cavities are closed, and, after a long period of drug treatment, the exudative part of the tuberculous lesion has disappeared, leaving in the x-ray film comparatively hard-looking strands and nodules. Hundreds of these residual lesions have been resected in the past few years, and in a high proportion of cases areas of necrosis are found and these areas often have small bronchial connections. Smears from the necrotic areas, particularly if taken from their walls, may show myriads of acid-fast bacilli, but as already mentioned these bacilli usually cannot be cultured or cause disease in laboratory animals.

Before the general subject of chemotherapy is closed it should be stated again that the end results of this treatment are not yet known. One writer has pointed out that when one compares the condition of patients discharged from sanatoriums in 1950, those who left in good condition, without having had drugs, have done as well as those who had streptomycin. But he does not note the relative numbers brought into condition for discharge by the two methods of treatment.

Reference should be made here to the recently published summaries of the extremely important studies on chemotherapy. The Veterans Administration study has been summarized.[66] The Trudeau Society has also reported its investigations.[67] The most recent report from the United States Public Health Service[68] gives the results of various drug combinations on 768 patients who continued treatment for a thirty-two-week period; a report on forty-week observations on 583 patients with streptomycin-susceptible infections had previously been presented.[69]

Streptomycin

Streptomycin, the original drug that started the new era in the treatment of tuberculosis, is still the agent of choice in most clinics and constitutes the standard by which the effects of all other drugs are judged. The original studies were on the use of streptomycin alone, but since 1950 streptomycin has always been thought of in combination with PAS. And for an easily comprehended figure one usually finds that the latest report of the Veterans Administration, Army and Navy conferences gives a careful study of 1500 patients who had the same results with streptomycin twice a week as with daily streptomycin and that the relapse rate to date is 5 per cent. Similar results are described in a study of 331 patients treated at the Trudeau Sanatorium.[70]

There is also a report by Rothstein and Johnson[71] suggesting that 2 gm. of streptomycin given once a week is almost as effective as 1 gm. given twice a week. Such a schedule is not recommended for general use but would be helpful in special circumstances.

Much discussion goes on about the relative merits of streptomycin and dihydrostreptomycin. It has been definitely proved that streptomycin may lead to vestibular damage and produce vertigo whereas dihydrostreptomycin is much more apt to cause auditory damage, the deafness being apt to appear where drug therapy has been continued for longer than six months or even after all drug treatment has been stopped. A dosage schedule of twice weekly rather than daily eliminates many of these toxic reactions.

Hinshaw has carried out a very interesting study on patients treated daily with a mixture of 0.5 gm. of streptomycin and 0.5 gm. of dihydrostreptomycin on the theory that a half dose of both would add up to the therapeutic benefit of a full dose of either and at the same time eliminate the toxicity of both. Results to date are impressive, but there is the possible danger of sensitizing patients to both forms of streptomycin when one form might be held for future use if necessary. However, patients resistant to one form are almost always resistant to the other.

PAS

Many interesting problems have arisen as the result of the use of PAS. It has very slight antituberculous activity of its own but has been extremely important if given with streptomycin by delaying the emergence of resistance to this vital drug. The chief difficulty is the high frequency of nausea and diarrhea accompanying its use. Under the best of conditions about 35 per cent of patients taking it have gastric disturbances. However, even this frequency of adverse symptoms does not keep most investigators from prescribing PAS with streptomycin or with INH instead of the much less upsetting combination of streptomycin and INH. Their argument, of course, is the importance of not giving the two best drugs at the very start of treatment. One should be saved, they say, for future use if necessary.

Sodium PAS seems to cause less disturbance than the regular form. The use of capsules is preferred by many. Recently, PAS has been given in association with a resin as Resipas.[72]

Recent studies have called attention to a problem hitherto considered of little importance, the development of resistance to PAS itself. This possibility should be considered when prolonged combined therapy seems to be losing its effect.

A very interesting possibility is the enlargement of the thyroid gland that frequently accompanies the use of PAS. There are three reports from England[73-75] and one of 11 cases from the Trudeau Sanatorium.[76]

Isoniazid (INH)

The point of greatest interest in the tuberculosis problem in the past two years has been the evalua-

tion of this new drug, which is easily manufactured, inexpensive and almost nontoxic, can be taken by mouth and is highly effective in combating tuberculous infection. Many questions have been raised concerning it, and much is yet to be learned.

As noted above, there is a controversy about whether this drug breaks what has come to be an accepted principle in the chemotherapy of tuberculosis: that a combination of drugs is always necessary. Such well known authorities as McDermott and Muschenheim believe that INH can well be used alone. They report[65] on 32 patients who were so treated for a year. At the end of this time there was a positive culture in only a third of the cases, and cavity closure had taken place in a third. In view of the type of case selected these results were considered as good as could be expected with any chemotherapy. It is suggested by various investigators that noncavitary cases offer the best prospects for single drug treatment.[77] However, Karlson and Feldman[78] report that in guinea pigs there is no question that better results are obtained with the combination of streptomycin and INH than with either drug alone.

The next point of interest is the dosage of INH. It is becoming apparent from both the experimental and clinical sides that a low dose is just as effective as a larger one. In this respect INH differs from streptomycin. There is apparently no gain in giving more than 150 mg. of INH a day, and with this amount there is almost no peripheral neuritis or the gastric disturbance that may occur with larger doses.

INH appears quickly in effective amounts in the spinal fluid and in the pleural fluid, and acts rapidly in stopping discharge from cutaneous tuberculous sinuses.[79]

Certain toxic symptoms charged to this drug are often associated with the larger doses. The symptoms are peripheral neuritis (especially in alcoholic patients), convulsions (almost always in epileptic patients) and hemoptysis (reported infrequently in this country).

An unsettled question relates to the virulence of tubercle bacilli that are resistant to INH. Steenken and Wolinsky[80] and others are inclined to believe that such bacilli, although viable, are not virulent.

Pyrazinamide (PZA) (Aldinamide)

Another very promising drug, pyrazinamide, has toxic possibilities. Its clinical use is still considered in the experimental stage, but it was ready for distribution to certain qualified hospitals in July, 1954. It has a definite initial appeal because of the ease with which it can be produced and its present estimated low cost of about 60 cents a day.

The first thing that confuses the status of PZA is the report from two reliable laboratories that it has very little antituberculous activity in the test tube or in the guinea pig[81,82] although it is effective in mice. However, the clinical trials are so impressive that one has to set aside, at least temporarily, these laboratory reports. In the original clinical trials when PZA was given alone the results were excellent for about six weeks, but at the end of this period resistance appeared, bringing with it a loss of further benefit. The addition of streptomycin failed to improve the result, but the addition of INH has given a remarkably effective plan of treatment. There is the advantage in this combination that both drugs are taken by mouth and have no unpleasant side effects.

The point that is holding back approval of the use of PZA is the danger of liver damage. McDermott and Muschenheim[83] treated 55 patients with 1 fatal drug-induced hepatitis on the fifty-fifth day of therapy. Five cases of nonfatal hepatitis were also observed. But it is hard to accept their conclusion that "the high incidence of hepatitis in man during pyrazinamide-isoniazid administration makes the use of this regimen in present dosage inadvisable as a treatment for tuberculosis" when they also make the following statement:

> . . . pyrazinamide-isoniazid exerts antituberculous activity *in vivo* of a sort superior to that of the other current antituberculous drugs used either singly or together. Moreover the animal studies indicate that the antimicrobial action of pyrazinamide-isoniazid is not only quantitatively superior but is qualitatively unique among antituberculous chemotherapies.

And their last report in the same journal for October, 1954, implies a change of heart.

It is a comfort to read the statement of Schwartz and Moyer[84] that "after two and one-half years of experience with 181 patients treated with pyrazinamide, either alone or together with PAS, streptomycin, or isoniazid, it has been necessary for the first time to discontinue pyrazinamide-isoniazid in 2 patients because of mild jaundice during the past month." Their 2.8-gm. daily dosage is only slightly smaller than the schedule of McDermott (50 mg. per kilogram of body weight). They report the results of PZA in addition to INH in 30 patients who had had no previous PZA or INH and were all streptomycin resistant. Of 19 patients treated for eight months 79 per cent showed marked or moderate x-ray change, 56 per cent demonstrated cavity closure, and 100 per cent had negative cultures.

Viomycin

This drug has been carefully studied by several very competent groups and should be given a definite place in the list of potent antituberculosis agents. It is less effective than streptomycin, isoniazid and pyrazinamide but should certainly be considered if resistance to these drugs has developed and further treatment is indicated.[85,86] Audiometry and studies of plasma electrolytes are necessary accompaniments of its use. It should be given intermittently, probably 2 gm. twice a week. All kinds of combinations with PZA, INH, PAS, tetracycline and oxytetracycline

have been suggested. Tucker has collected reports on 125 patients from 16 different Veterans Administration hospitals but has not yet presented the results. In about 15 per cent of cases viomycin was stopped because of toxic reactions. Recently, 2 patients had anaphylactic shock.

Oxytetracycline (Terramycin)

This drug is also on the "approved list" for special uses. Most of those who have had experience with it have recommended its administration with streptomycin in place of PAS. Given in this way it seems as effective as PAS and has fewer troublesome side effects. There has been much discussion about dosage, the Fitzsimons group believing that 2 gm. a day does not give the complete protection against the emergence of streptomycin-resistant tubercle bacilli that is obtained with 5 gm. daily.[87] Some workers believe that 1 gm. of oxytetracycline a day is as good as PAS, and they are content with that. Interesting observations are coming from the laboratories regarding drug combinations, and one of the most interesting on oxytetracycline is the report[88] that when that drug and isoniazid are used together the bactericidal action of isoniazid is almost completely inhibited. The authors conclude that "the bacilli whose multiplication is prevented by . . . [oxytetracycline] are insensitive to isoniazid and the latter drug is probably only bactericidal for tubercle bacilli in an active metabolic state." One report blames oxytetracycline for an almost fatal case of staphylococcal enterocolitis, but in general the clinical toxicity seems very low.[89]

At this point it might be stated that the general opinion is that two drugs are almost always enough and that triple therapy is rarely indicated. However, some authorities disagree.

Childhood Infection

In recent years the question has arisen whether one should give chemotherapy for what used to be called the "benign, childhood type of infection." But even years ago the dangerous character of infection in at least the first two years of life was recognized and the plea now is to give chemotherapy for both early and late childhood infections and thus to prevent meningitis, which has been all too frequent in children in the past. Dr. Edith M. Lincoln,[90] of Bellevue Hospital, who has had extensive experience with tuberculous infection in children, reports that for the period 1930 through 1946 the mortality in primary pulmonary tuberculosis was 21.5 per cent. This fell to 5.0 per cent after the introduction of streptomycin combined with Promizole or PAS. Since the introduction of INH in 1952 the rate has fallen to 1.5 per cent.

Ambulatory Chemotherapy

After the problem of what drug or combination of drugs is best for a particular person with a particular kind of tuberculous infection has been settled and his previous treatment assessed, the next major consideration is the amount of rest necessary in addition to the drugs. And one must be prepared to put aside at least temporarily the dictum of the past fifty years that a great deal of rest is necessary for every case. Very few doctors allow patients to be out of bed so long as they have fever, but once the febrile stage is safely over the race for complete activity begins. Therefore, the rest program should be evaluated with allowances for personal prejudices and experiences.

Because the bed rest at the Channing Home in Boston has been unusually complete a report from that institution by DeFriez et al.[91] is first considered. The strictest kind of bed rest was carried out on 377 consecutive patients admitted between 1930 and 1944 and followed for not less than five and not more than twenty years. The cumulative relapse rate was 39.1 per cent for minimal and 56.2 per cent for advanced tuberculosis; 70 per cent of all relapses occurred within five years of discharge. It was concluded that strict bed rest was not superior to modified bed rest.

Modified bed rest in "active uncomplicated minimal pulmonary tuberculosis" among 4926 patients admitted to the Trudeau Sanatorium[92] from 1927 to 1946 has been described. It should be noted that this program applied only to the minimal cases, numbering 589. The author concludes that in these cases modified bed rest alone failed in 27.6 per cent "to prevent progression to advanced disease during a projected twenty year follow-up period."

Likewise from the Trudeau Sanatorium comes a report[93] on 152 patients with "active minimal" disease treated in a slightly earlier period (1921 to 1929) by combined rest and exercise and reviewed in 1951-1952. At this time 84 per cent were well and working when last heard from, and 72 per cent were well and working twenty to thirty years after discharge; 7.8 per cent had died of tuberculosis. The authors conclude that "the results of this form of treatment compare favorably with the results obtained by strict and modified bed rest as reported in the literature."

Next, if one takes it for granted that a certain period of rest is necessary, how much time should be spent in a sanatorium? If the sanatorium waiting list is long it may be best to start chemotherapy while the patient is still at home. But, in spite of the emotional and financial problems involved, most physicians experienced in the care of tuberculosis agree that it is best to have at least a preliminary period of sanatorium care, with a chance to know about other patients, and to talk to those who are going through an experience similar to their own, in a place where the different methods of treatment can best be evaluated for the individual case. It must be admitted that once in a sanatorium patients find it hard to get out and that sanatorium physicians are

perhaps inclined to hold patients "for safety's sake." Only further time and experience can determine the optimum duration of sanatorium care.

Chapman, after a wide experience in Detroit (results not yet published), reports informally but favorably on 1468 patients discharged after four months of chemotherapy in sanatoriums.

An interesting comparison (as yet unpublished except in *Veterans Administration Quarterly Reports)* between "old-fashioned sanatorium rest" and the Sunmount plan of early ambulation has been carried on for over three years between the Veterans Administration Hospital in Minneapolis and Sunmount itself. One must not draw conclusions from this early report, but it is at least interesting that the rate of relapse in the two groups was the same (about 5 per cent) in spite of the fact that the Sunmount group had at least four or five hours a day more out-of-bed activity than the Minneapolis group, who had practically none.

It is important to realize also that the Veterans Administration has authorized "antituberculosis chemotherapy on an outpatient basis" only "as a direct continuation of a treatment program initiated during the hospitalization of the beneficiary concerned."

Finally, it should be recorded that the Committee on Therapy of the American Trudeau Society[94] reports that there "appears to be no doubt that antimicrobial therapy has materially shortened the period of recovery [but that] this does not necessarily imply . . . that it has altered the indications for rest therapy during the active phases of the illness." This means "relatively complete bed rest—until all symptoms have cleared, all cavities have been lost to view roentgenographically, all regressive infiltrations have reached an unchanging status, and sputum and gastric washings have become negative for tubercle bacilli by direct examination and culture."

Miliary and Meningeal Tuberculosis

The most convincing proof of the value of streptomycin is the unquestioned saving of lives of certain patients with proved tuberculous meningitis, a disease previously 100 per cent fatal. It must be remembered that in miliary tuberculosis, without meningitis, there was a small percentage of recovery even before chemotherapy.

The statistics on the treatment of meningitis are confusing because so many different drugs and drug combinations have been used, and because a comparatively new drug, INH, has been shown to be so much more effective than any other.

The Veterans Administration's figures on meningitis (reported in February, 1954) are the most helpful ones now available. The total number of cases treated since 1946 is 670 miliary and meningeal. At the end of eighteen months the survival rate was 23 per cent for 122 patients with meningitis only, treated with streptomycin alone, 15 per cent for 39 cases with streptomycin and Promin, 51 per cent for 87 cases with streptomycin and PAS, and 81 per cent for 39 cases with streptomycin and INH.

Dr. Edith M. Lincoln, who has had wide experience with meningitis in children, reported in 1953 that with streptomycin combined with Promin and INH she had had only 1 death in 11 cases followed for six months or longer. On streptomycin and Promin there had been 16 deaths in 48 cases.

There has been considerable disagreement about dosage and duration of treatment, but daily treatment for a long period seems essential. The tendency is to continue treatment for about eighteen months. Drug resistance is rare in meningitis without active pulmonary tuberculosis.

Early treatment is essential, and it is believed that the process is reversible during the first three weeks of illness. It is on this account that certain writers have advised ACTH or cortisone for this three-week period.

Miliary tuberculosis is dangerous because of the possibility of a later meningitis. In the Veterans Administration series (which did not, of course, include children) meningitis developed in 73 out of a total of 277 cases of miliary disease. In a later report there were 89 patients with miliary disease, all treated with INH, and after twelve months none had meningitis.

The outlook is unbelievably better than it was in October, 1952, when the Bellevue Hospital reported only 4 survivors out of 60 patients who had been on various chemotherapy regimens.[95]

ACTH and Cortisone

Mention has already been made of the possible value of these substances in the treatment of meningitis. Further notes should be recorded about other possible uses. Two reports on experiments at Duke University[96,97] state, first, that cortisone alone exerted an enhancing effect on the pathologic process in rabbits, but that this effect was overcome by the addition of streptomycin; and, secondly, that ACTH had no damaging influence on the course of untreated tuberculosis, nor did it interfere with the beneficial healing effect of streptomycin.

There is also an interesting paper from England[98] stating that combined ACTH and chemotherapy gave pronounced clinical improvement in 21 patients, with no bad withdrawal effects, and that in 8 of these patients it eliminated serious allergic reactions to streptomycin or PAS or both.

Minor Items

Iodides

The question of whether iodine has a bad effect on the tuberculous process in human beings has long been debated. In a collection of opinions of 21 students of tuberculosis made by Dr. John R. Mote

most of the writers admitted lack of evidence for a good opinion but believed it safe to use iodides, at least in moderation.[99]

A very informative article regarding the use of potassium iodide in combination with streptomycin in the treatment of experimental tuberculosis in the guinea pig was written by Hamilton and Geever.[100] Their conclusions were as follows:

> . . . in unvaccinated animals potassium iodide appeared to be detrimental to the success of treatment with an adequate dose of streptomycin. In guinea pigs previously vaccinated with B.C.G., potassium iodide augmented the efficacy of streptomycin.

As applied to human patients this suggests that streptomycin combined with potassium iodide would be helpful in a chronic form of tuberculosis but dangerous in acute tuberculous infection.

It is interesting that comparable results were reported in patients who had intratracheal installation of lipiodol during x-ray studies. In a study[101] of 49 patients bronchogenic spread occurred in those with "unstable, progressive lesions" but not in those with "a favorable resistance-infection relationship."

Alcoholism

Without giving details it should be stated that alcoholic patients are apt to leave sanatoriums against advice (28 per cent of such discharges in one report) and that alcoholism certainly predisposes to neurotoxic symptoms during INH therapy.

Erythema Nodosum

Reports on cases of erythema nodosum due to tuberculosis continue to appear. In this country tuberculosis still seems a less frequent cause than elsewhere. An apparent source case of tuberculous infection in a village of 1500 in New Brunswick[102] was responsible for 12 cases of erythema nodosum, 16 pleural effusions and 14 cases of active pulmonary tuberculosis.

In a report from the United States[103] 105 cases are described. Fifty-five were thought to be of tuberculous origin, the infections in the remaining 50 patients, who had persistently negative tuberculin reactions, were thought to be due to the hemolytic streptococcus.

Erythema nodosum is said to have developed in 3 children of a tuberculous mother in England.[104]

Swimming-Pool Granuloma

There are two reports, one on a single case[105] and one on 9 cases,[106] of a granuloma resembling a tuberculous infection that appeared after abrasions on the bottom of swimming pools. There was no definite proof of tuberculosis.

Banked Bone

In these days of "bone banks" attention should be called to a report[107] of the use of ribs removed at thoracoplasty for pulmonary tuberculosis. In 4 cases tuberculous abscesses developed after the use of such ribs.

Chronic Descending Pulmonary Tuberculosis

As one follows various types of tuberculosis in the lungs one is impressed by the occasional case that starts as fine mottling at the tops of both lungs and has a slow but relentless downward spread during several years. This condition deserves attention because chemotherapy is particularly effective in stopping the spread.[108]

Bovine Tuberculosis in England

In these days when bovine tuberculosis is almost unheard of in the United States it is important to note a report from England[109] of a study of 994 cultures of tubercle bacilli obtained from patients; 261 (26.3 per cent) of these were of the bovine type.

Conclusions

As one reviews the literature on tuberculosis one keeps wondering why the infection is so well controlled in most human beings who receive tubercle bacilli into their bodies, and what brings about an active process in a certain proportion of cases, changing "tuberculous infection" into "tuberculous disease." At least five conditions seem to have a direct bearing on such a change: starvation; gastric resection; cortisone administration; diabetes; and puberty. Is there a common factor in these conditions?

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MEDICAL INTELLIGENCE

TOPICAL USE OF TRIPELENNAMINE IN UROLOGIC PROCEDURES*

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THE need for a relatively nontoxic topical anesthetic agent in cystoscopy becomes apparent when one checks the literature on the various reactions[1-5] reported with the anesthetics now in use. Our own experience has also indicated this need.

Since the mucous membrane of the urethra has a highly efficient absorbing surface manifestations of toxicity have occurred with disturbing frequency after application of certain local anesthetics.[6] In some patients sensitivity to available local anesthetics has even made it necessary to carry out urethral manipulations without the use of such agents.[6]

Recently, in an eighty-three-year-old man with renal-cell carcinoma, 10 cc. of a 4 per cent solution of piperocaine was instilled before a retrograde pyelogram. Almost immediately twitching of the facial muscles followed by violent contractions, cyanosis and dyspnea developed. This disturbing incident led us to try tripelennamine§ anesthetic solution (2 per cent) as a possible replacement for the local anesthetics we were using, since a survey of the literature had demonstrated the value of tripelennamine hydrochloride (widely prescribed as an antihistamine) as an effective and relatively safe topical anesthetic.

The topical anesthetic properties of tripelennamine were noted incidentally by Rennick and her coworkers[7] in the laboratory during early toleration studies, before clinical appraisal for its antiallergic potentialities. They found that holding tripelennamine crystals between the lips resulted in anesthesia

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§Kindly supplied as Pyribenzamine Anesthetic Solution by Ciba Pharmaceutical Products, Incorporated, Summit, New Jersey.

of the medicated areas within three or four minutes. In the majority of cases this effect lasted for fifteen to thirty minutes. Yonkmann et al.,[8] in a later study, produced anesthesia in the exposed sciatic nerve of the frog by applying cotton pledgets soaked with a 2 per cent tripelennamine solution.

In 1948 Moseley[9] used a 1 per cent solution of tripelennamine as a gargle and mouthwash to anesthetize the oral and pharyngeal mucosa. At that time he stated, "With further observation it may prove safer to use this drug Pyribenzamine for this purpose than to use some of the now more generally used topical anaesthetics." Landau, Nelson and Gay[10] found "antihistaminic compounds had . . . from 2.4 to 4 times as much anesthetic effect as procaine in the human skin."

TABLE 1. *Types of Examination.*

EXAMINATION	NO. OF CASES
Cystoscopy & urethroscopy	180
Cystoscopy & dilatation	15
Retrograde pyelography	65
Retrograde pyelography with retroperitoneal air insufflation	4
Ureteral dilatation	2
Bladder biopsy	9
Ureteral meatotomy & loop manipulation	1
Total	276

In clinical urologic studies Fitzpatrick and his associates[6] reported 50 cases in which a 2 per cent solution of tripelennamine was employed for urethral manipulation. They stated that it was more effective than 4 per cent piperocaine hydrochloride. According to the authors, "the use of tripelennamine hydrochloride as a local anesthetic agent will produce excellent anesthesia in cystoscopic examinations particularly where there is active bleeding or where patients demonstrate an idiosyncrasy to the usual agents."

Reynolds, Kahn and Levy[11] commented on the duration of tripelennamine anesthesia, noting that "the effect . . . persists approximately an hour, sufficient time to make the examination in a leisurely manner."

With this accumulated pharmacologic and clinical evidence of the efficacy of tripelennamine as a topical anesthetic, it was decided to use a 2 per cent tripelennamine solution in various urologic procedures; 15 cc. of a sterile stock solution was instilled five minutes before introduction of the cystoscope.

Two hundred and seventy-six examinations were made on 266 patients ranging in age from fourteen to eighty-four, with an average age of sixty-one (Table 1). Results were considered good if there were no complaints on instrumentation, fair if there was slight pain or discomfort on passage of the instrument into the posterior urethra and poor if there was pain on passage of the instrument or during the examination, or both.

As Table 2 indicates, the 2 per cent solution had a good effect in 160 cases, or 58 per cent, and a fair effect in 84, or 30 per cent; only 32, or 12 per cent, showed poor results.

The only side effect observed, occasional slight burning on instillation of the solution, disappeared as the anesthesia deepened. The effect lasted for forty to sixty minutes, allowing ample time for a thorough examination.

Five patients who had had previous multiple cystoscopies with other anesthetic agents mentioned that, as far as pain was concerned, the new drug was as effective as or better than those used before.

SUMMARY AND CONCLUSIONS

The mucous membranes of the genitourinary and gastrointestinal tracts, as well as of the bronchi, have a highly effective absorbing surface. This may account, at least in part, for the severity of reactions encountered with certain topical anesthetics in various endoscopic procedures. Our experience with reactions to certain topical anesthetics in cystoscopy is similar to that of other urologists.

Reports in the literature have demonstrated that, as a group, antihistaminic compounds have a potent local anesthetic effect. Clinical studies on the use of a 2 per cent tripelennamine anesthetic solution in 276 urologic examinations indicated that this preparation is a relatively safe and effective topical anesthetic. There were no disturbing side effects. The anesthetic effect lasted from forty to sixty minutes, permitting ample time for examination.

In our opinion the 2 per cent tripelennamine solution compares very favorably with other topical anesthetic agents used for urologic procedures. It is to be noted in particular that the excellent tolerance for this solution led us to employ it in the presence of urethral bleeding, a circumstance that had previously been considered a contraindication to topical anesthesia.

TABLE 2. *Results with 2 Per Cent Tripelennamine Anesthetic Solution.*

RESULT	NO. OF CASES
Good	160(58%)
Fair	84(30%)
Poor	32(12%)
Total	276(100%)

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BY THE LONDON POST

The Common Health — Centenary at St. Mary's Hospital — The Doctor and His Car

JOHN LISTER, M.D.

LONDON, ENGLAND

EVER since 1901, when King Edward VII graciously consented to become patron of the British Medical Association, the Association has been honored by the patronage of each successive sovereign. Today, it rejoices in the patronage of Her Majesty, the Queen, and at a recent Council Dinner the Duke of Edinburgh, the principal guest, graciously accepted honorary membership in the Association. In conferring this membership on the Duke, the chairman of the Council, Dr. E. A. Gregg, recalled how His Royal Highness had continually shown his interest in the welfare of the people and in the practical application of scientific knowledge. In his presidential address to the British Association three years previously he had urged that scientific knowledge be used "to set the world free from drudgery, fear, hunger and pestilence."

Thanking Dr. Gregg, the Duke said that he would not take advantage of his position as an honorary member except that he would continue to disagree with doctors when he felt like it. He then proposed the toast of the Common Health. In doing so he said that he was sure that the Common Health is more than figures showing improved birth rates, death rates and the incidence of disease. In particular he stressed the importance of the individual. He said that much of the progress in medicine has been made at the price of deeper and narrower specialization, but the individual is still one unit. He was all for studying bits and pieces, but he hoped that treatment could remain directed to the whole.

Replying to the toast, the minister of health, Mr. Iain Macleod, said that the Duke of Edinburgh, by his leadership of the National Playing Fields Association, had done as much as anyone to encourage the active interest in physical well-being that is the foundation of good health. Mr. Macleod appealed for a more positive approach to good health; one must seek it and cherish it and do everything one can to have a service in this country that not only sets out to cure ill health but does its best to promote good health. He expressed a similar point of view in his introduction to the Ministry of Health report for 1953, in which he stated that in the first five years of the National Health Service the initial problems had been tackled with spirit and with a united effort though much remained to be done. During the past year the nation's health statistics have shown a further reduction in mortality from tuberculosis, the virtual disappearance of typhoid fever as a public-health problem and the practical elimination of diphtheria. On the debit side there has been a continuation of the "mysterious and inexorable march" of carcinoma of the bronchus, which continues to claim an additional thousand victims a year. Mental illness is cited as one of the great despoilers of the working capacity of the nation, and the report stresses the importance of education and preventive psychiatry in this field. Indeed, it seems that many of the gaps between scientific discovery and the promotion of the Common Health can only be bridged by the education of the people.

* * *

Although St. Mary's is one of the youngest of London's medical schools, it has just celebrated a century of great achievement. The school has a varied history and a distinguished record in the field of medical research. It was there that Alexander Fleming discovered penicillin, Leonard Colebrook worked on the treatment of puerperal fever and Augustus Waller laid the foundation of electrocardiography.

It is also interesting to note how great a part the sports grounds have played in the lives of the students of St. Mary's. Indeed, it has been said that the Battle of Waterloo was won on the playing fields of Eton College, and it might be said that the battle of the microbes has at least been fought on the playing fields of St. Mary's.

In the last twenty years, while 5 of their graduates have been elected fellows of the Royal Society, 4 have been chosen to captain the English Rugby Football International team. This year, too, the hospital had the outstanding honor of claiming Dr. Roger Bannister, a graduate of the school, as the first man to achieve the four-minute mile.

At the recent centenary celebrations Queen Elizabeth, the Queen Mother, laid the foundation stone of a future centenary wing. Inside the hollows of the stone, with glass covers for all to see, she then placed five tokens of the school's achievements: a signed history of the school, presented by the author, Sir Zachary Cope; a copy of the day's proceedings; an illuminated list of the school council, staff and students; and two final objects that brought forth the greatest burst of applause from the gallery filled with students. The first was a stop-watch indicating the time (3

minutes 59.4 seconds) that Roger Bannister took to run his mile, and the second was a penicillin-culture plate presented by Sir Alexander Fleming. These objects seem to symbolize the past and present and a challenge for the future.

In her speech the Queen Mother expressed the hope that St. Mary's would be able to increase its accommodation by the erection of the new centenary wing and to extend its outstanding work in the field of medical education and medical research.

* * *

Physicians have been enthusiastic motorists since the early days of motoring. It is only natural that this should have been so, for the advent of the motor car provided them with a greatly improved method of visiting their patients.

In this country, if a group of doctors are not talking about their work, they are sure to be talking about motoring. If the discussion is not concerned with the past, present or future automobiles of those present, it doubtless concerns the huge size and expensive make of car that some more successful physician has just purchased.

Unkind things have been said about the doctor and his car. He was accused of being privileged when he was able to obtain gasoline during wartime rationing, when he was able to purchase a new automobile on a priority docket or when he seemed able to afford a larger car than his lawyer neighbor. Nevertheless, the modern doctor must have a car, and if he thinks a Rolls Royce is more reliable than an Austin, he must have a Rolls Royce; if he thinks a Cadillac is more reliable than say a Ford, he must have a Cadillac because, after all, it is only the patients who will benefit!

For the real enthusiast the snag about modern motoring is that it has become so dull. Gone forever are the sporting gear changes as the lever on the floor is being replaced by the automatic change. Gone too are the joys of "swinging the old bus" because the starting handle (crank) is congenitally absent on many new makes. This seems to be tempting providence just too far, and some doctors will not buy a car that they cannot "swing" if need arises.

But, quite apart from the car itself, the most pressing problem today is how to use it. The roads are becoming more congested, and parking space is becoming more limited. New parking bans have been imposed in London, and the British Medical Association has advised doctors who have difficulty in parking to seek police assistance. The police authorities have refused to grant any special dispensation to allow doctors to park in forbidden areas, but they have agreed to help them find parking space as near their patients as possible.

The result of all this is that perhaps after all the large, sleek limousine is not the height of professional ambition. Perhaps the small, modest, fuel-saving baby car is easier to manipulate in traffic, easier to park and cheaper to run. Indeed, it may be that soon the full circle will be completed and it will be easier still to walk!

CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 41041

PRESENTATION OF CASE

First admission. A thirty-five-year-old man was admitted to the hospital because of pain in the lower abdomen, anorexia, fever, malaise, repeated vomiting and dark urine.

Eight days previously, after his usual large breakfast, he was suddenly seized with malaise, anorexia and a severe chill. He returned home from work with his teeth chattering and then noticed cramping pains in the lower abdomen that were not relieved by an enema or much influenced by food. The temperature at that time was 100°F., and, for the next week, until admission, it fluctuated between 99 and 102°F. For the first five days of illness he vomited almost every time he ate, the vomitus being greenish, thin and without blood. He had noticed the appearance of dark urine three days before admission. The generalized symptoms in the lower abdomen subsided about three days before hospitalization, and then right-lower-quadrant tenderness developed. There had been no back pain, bloody stools or urinary symptoms.

For three years he had had infrequent episodes of burning, boring, epigastric pain radiating to the back, disturbing when he was hungry and relieved by food and rapidly by alkali. No anorexia or weight loss had occurred. X-ray films a year before admission confirmed the presence of a gastric ulcer and on x-ray examination a month later, after a bland diet, Amphojel, and some (mouth-drying) pill, the ulcer appeared smaller. During the past year, the symptoms had been fairly easily controlled by this regimen, and in recent months the patient had taken very little medication but adhered to his diet.

Physical examination revealed an obviously ill man who was not, however, in any acute distress. The scleras were icteric. Examination of the heart and lungs was noncontributory. There was definite right-lower-quadrant tenderness, well localized with some spasm. Rectal examination revealed moderate tenderness across the pelvic floor, but no definite mass could be felt.

The temperature was 101°F., the pulse 110, and the respirations 20. The blood pressure was 130 systolic, 75 diastolic.

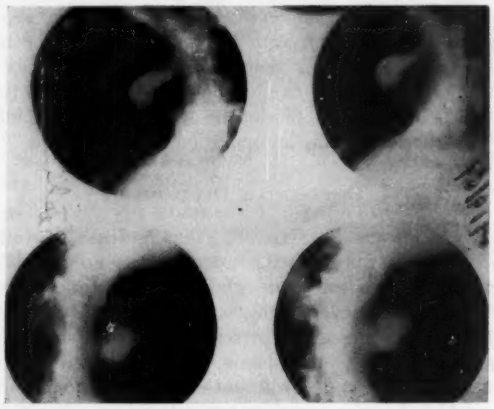

FIGURE 1. *Pressure Spot Films of Lesser-Curvature Aspect of Stomach, Showing Huge Penetrating Ulcer Crater.*

Urinalysis showed a specific gravity of 1.031, a + + test for albumin, a negative test for sugar, a + test for bile and rare cells in the sediment. Blood studies revealed that the hemoglobin was 14.2 gm., and the white-cell count 16,200, with 78 per cent neutrophils, 12 per cent lymphocytes, 4 per cent monocytes and 3 per cent eosinophils. One day later the white-cell count was 25,800. The blood Hinton test was negative. The nonprotein nitrogen was 22 mg., the total protein 6.8 gm. with an albumin-globulin ratio of 1.3, the alkaline phosphatase 4.2 mg., and the bilirubin 3.6 mg. per 100 cc. The prothrombin time was 100 per cent. A stool was guaiac positive. An x-ray film of the chest was normal, and a plain film of the abdomen showed no masses or definite abnormality.

The patient was treated conservatively and by the third hospital day there was subjective and objective improvement in his condition; the white-cell count had fallen to 18,500, but the temperature remained elevated around 100°F. He continued to improve gradually, and, after a week in the hospital, x-ray studies of the gastrointestinal tract were performed. The barium-enema examination was suggestive of extrinsic pressure on the anteromedial aspect of the cecum. The upper gastrointestinal series disclosed a penetrating gastric ulcer, 2 cm. in diameter, on the lesser-curvature aspect above the angle (Fig. 1). A small-bowel study was not remarkable. Subsequent laboratory studies on the tenth day showed a further drop in the white-cell count to 8700, an alkaline phosphatase of 9.5 mg. per 100 cc. and a cephalin flocculation of + + + in twenty-four and forty-eight hours. A gastric analysis revealed no free hydrochloric acid but 60 units of acid half an hour after the administration of histamine. After two weeks of medical management the symptoms subsided, including the temperature, which returned to normal on the tenth day. He was discharged on an ulcer regimen to return eventually for a gastrectomy.

Second admission (two months later). He had been well in the interim; the sudden onset of pains in the lower abdomen led to this admission.

Physical examination revealed a diffusely tender lower abdomen, with spasm and rebound localized tenderness in the right lower quadrant. Peristalsis was diminished. Rectal examination revealed slight tenderness but no mass.

The temperature was 102°F., the pulse 110, and the respirations 20.

Urinalysis showed a + test for albumin and 4 white cells and occasional red cells per high-power field in the sediment. The white-cell count was 15,400. A barium-enema examination again revealed a definite pressure defect on the medial wall of the cecum and fixation and extrinsic pressure on the right lateral margin of the sigmoid (Fig. 2). An upper gastrointestinal examination showed the lesser-curvature gastric ulcer, which was smaller in size; the mucosa around the base of the ulcer was considered to be normal (Fig. 3 and 4).

FIGURE 2. *Film from Barium-Enema Examination. Arrows point to pressure defects on the cecum and the sigmoid loop.*

Shortly after admission the patient had a chill. On the same day a thick, stiff-walled abscess enclosed by the cecum, small bowel and sigmoid was drained, and a six-day course of streptomycin and penicillin therapy started. A bacteriologic culture of the drained material was negative. Tenderness, edema

FIGURE 3. *Film from Gastrointestinal Series. Arrow points to penetrating ulcer seen in profile, extending from the barium-filled stomach.*

and redness persisted in the operative region, requiring further incision and drainage twelve days later. After this, improvement was sufficient to allow the patient to be discharged asymptomatic on a low-

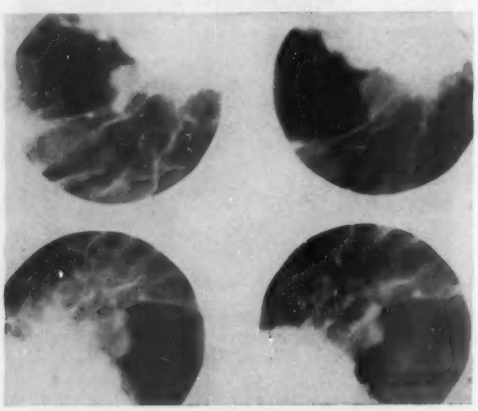

FIGURE 4. *Pressure Spot Films of the Stomach. Note smaller ulcer crater and large gastric rugae.*

roughage diet after a twenty-five-day stay in the hospital. Before discharge, stool studies for parasites were negative. The cephalin flocculation was negative in twenty-four and forty-eight hours.

Third admission (one month later). The patient had lost 15 pounds in weight, felt ill and had occasional mild abdominal colic. He was readmitted for an interval appendectomy.

The temperature was 99°F., the pulse 90, and the respirations 20. The blood pressure was 120 systolic, 70 diastolic.

Physical examination revealed some increased resistance and mild tenderness in the area of the right-lower-quadrant incision. No mass was palpable, however. Rectal examination was suggestive of an indefinite, tender mass high in the right side of the pelvis.

Urinalysis was negative. The white-cell count was 14,500, with 65 per cent neutrophils, 25 per cent lymphocytes, 4 per cent monocytes, 5 per cent eosinophils and 1 per cent basophils. Cephalin flocculation was + in twenty-four and ++ in forty-eight hours. A plain film of the abdomen was normal.

On the second day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. RICHARD H. SWEET*: This patient's first admission was for an acute abdominal condition. In my experience an acute abdominal condition first manifested by severe chills is not at all frequent. A chill usually means the presence of an overwhelming infection such as pneumonia, pylephlebitis, liver abscess or acute endocarditis. Osler mentioned a chill and high fever as occasional manifestations of appendicitis. I have occasionally seen that myself, particularly if there is an early thrombosis of the appendiceal vein and a pylephlebitis.

In any acute abdominal condition the time relation of the onset of pain to other symptoms is important in diagnosis. Pain almost never follows the nausea and vomiting in acute appendicitis; on the contrary it precedes it, and I am therefore inclined to believe that this patient did not have appendicitis but some other condition. Also, I should like to stress the fact that the pain was in the lower abdomen, which is another indication that the lesion was not in the appendix, the small bowel or the gall bladder. Pain in this area is usually referred from the colon. If the pain had developed from localized peritonitis, it would have been confined to the region of the source of the peritonitis rather than generalized. As a matter of fact, the inflammatory lesion apparently later did become localized in the right lower quadrant. Physical examination confirmed the impression that there was an acute inflammatory process, first generalized in the lower abdomen and then localized to the right lower quadrant, where there was spasm, tenderness and a sensation of a mass.

The only features of the history up to the time of admission that an acute peritonitis localized to the right lower quadrant would not explain are the dark urine and the episodes of epigastric pain of three years' duration. Presumably, this pain was due not

*Visiting surgeon, Massachusetts General Hospital.

to a gastric carcinoma but to a peptic ulcer because the lesion showed a tendency to heal on a medical regimen.

The white-cell count at one time was at the level that one would expect with necrosis of tissue. In addition the patient had jaundice, which is difficult to reconcile with the symptoms and signs confined to the right lower quadrant. Could an inflammatory lesion in the upper abdomen secondary to an ulcer have perforated locally and caused an abscess in the region of the common duct, or the pancreas, with swelling and partial occlusion of the common duct, and then gravitated into the lower abdomen? That sounds unlikely in view of the subsequent developments, particularly the location of the abscess in the lower abdomen. Pancreatitis too seems unlikely, for with that the pain is usually in the upper abdomen and tends to radiate to the back. Acute cholecystitis, with or without gallstones, is not accompanied by jaundice unless there is cholangitis, a stone in the common duct or an associated pancreatitis with swelling and occlusion of the papilla of Vater.

Apparently, since there was no evidence of cholecystitis, pericholecystic abscess, pancreatitis or anything else, the physicians decided that the ulcer was the cause of the symptoms, and treatment for the ulcer was therefore given and a gastrectomy planned.

May I see the x-ray films taken during the first admission?

Dr. John F. Gibbons: The film of the abdomen taken soon after the admission does not show anything remarkable. The gas pattern is normal, and the viscera are apparently of normal size and shape; no masses are visible. Two days later the barium-enema examination was done, and the indentation on the anterior medial wall of the cecum, both when it was filled with barium and distended and after evacuation, was seen (Fig. 2). That is shown best in the spot films, which were made with the patient's left side forward because the indentation was on the anterior surface of the cecum. There is also a suggestion of fixation of a sigmoid loop, which does not contract and which has an unusually straight vertical position, and of a slight indentation on the medial wall. On the next day the upper gastrointestinal tract and the small bowel were examined. A large, penetrating gastric ulcer was found on the lesser curvature above the angle. The base of the ulcer has a persistent rim of decreased density, which was interpreted as being edema around the base of the huge crater (Fig. 1). It was thought that the folds leading to the base of the ulcer were normal. There is no evidence of abnormality in the gastric walls away from the ulcerated area. The pertinent films of the small-bowel examination show that there may be an indented area in the terminal portion of the ileum that was not mentioned in the protocol; I am not sure that it is a persistent indentation. The remainder of the small bowel appears normal, and there is no evidence of intrinsic small-bowel disease.

Dr. Sweet: Is there any evidence of perforation of the ulcer?

Dr. Gibbons: No; there is not.

Dr. Sweet: I cannot believe that the right-lower-quadrant difficulty bore any relation to the ulcer, which had been present for a long time. The onset of the difficulty was not that of a perforation. Moreover, since it was a penetrating ulcer of the posterior wall, if it had perforated, it would have perforated into the lesser omental bursa, and this should have been obvious in the x-ray films. It would have gravitated down the right gutter, but the residual abscess, for which there was evidence in the physical examination, was not in the gutter but medial to the cecum. I cannot believe, therefore, that the localized abscess in the right lower quadrant that I assume he had had anything to do with the stomach, gall bladder or any viscus in the upper abdomen. It must have arisen from a lesion in the lower abdomen, such as a perforated Meckel diverticulum, diverticulitis of the sigmoid, for which there was no evidence in the x-ray films, or appendicitis, the most common cause of such an abscess.

Two months later the patient was readmitted to the hospital, with pain in the lower abdomen, and had chills on admission. The chills are very significant, but I do not know how to interpret them. Of course in a young man with a disorder in the region of the appendix, I should suspect a repetition of appendicitis, with an appendiceal abscess. I have seen patients with appendiceal abscesses on whom we have delayed operation so that the abscess could clear up who have had an acute appendicitis with formation of another abscess in the interval. On physical examination this patient had evidence of another peritoneal insult. A temperature of 102°F. in a patient with appendicitis means perforation. Moreover, the most common cause of an abscess confined by the cecum, small bowel and sigmoid is a ruptured appendix. Other conditions that may cause such an abscess are a perforated Meckel diverticulum in rare cases and perforation of a diverticulum of the sigmoid.

That a culture of the material drained from the abscess was negative does not mean that it was not infected. The culture may not have been planted promptly enough.

The tenderness, edema and redness may or may not have been significant. I do not have to assume that there was something peculiar like actinomycosis. There may have been a technical fault with the effectiveness of the drainage to explain the necessity for reoperation.

Studies for parasites in the stool were done, but I do not know what parasites were sought.

Dr. Daniel S. Ellis: The patient had been in the South Pacific for three years and had had diarrhea.

Dr. Sweet: That was only to eliminate an underlying parasitosis.

Jaundice was not mentioned during the second ad-

mission. It had apparently cleared up after the first admission and had not recurred.

At the time of the third admission, the assumption had been made, I think properly on the evidence, that all the disease was from appendicitis. In addition there may have been a moderate degree of partial small-bowel obstruction because a loop of small bowel was involved. The mass high in the right side of the pelvis could well have been a secondary abscess, which would not be at all unusual with an abscess arising in the right lower part of the abdomen, particularly if that abscess had not been adequately drained.

Could the abdominal difficulty have arisen from an intrinsic disorder of the small bowel like regional enteritis? That is a possibility. A more remote possibility is a malignant tumor — a carcinoma or lymphoma — in the small bowel, with perforation.

May I see the x-ray films taken during the third admission?

DR. GIBBONS: We at no time thought that there was any evidence of regional enteritis or intrinsic small-bowel disease by x-ray examination. At the time of the second admission there is again the indentation on the medial wall of the cecum, and fixation and indentation of the sigmoid. These changes do not look much different from the way they did at the time of the first admission. At this time there is projecting from the lower edge of the cecum a small, stalklike excrescence filled with barium that we assumed was an appendix that had become necrotic and amputated itself. The studies of the upper gastrointestinal tract show the gastric ulcer in the same area (Fig. 3 and 4).

DR. SWEET: It appears to be much reduced in size.

DR. GIBBONS: It seems to be smaller than it had been three months previously. Again, the rugal folds up to the base of the ulcer in all projections were thought to be normal, and there again seems to be a broad band of edema around the base of the crater. In this film, which was taken at the end of the small-bowel examination, there is some abnormality in the distal ileum and appendix that we thought was due to extrinsic pressure and fixation.

DR. SWEET: One possibility that I have not mentioned is a gallstone passing down the common duct and ulcerating into the duodenum or stomach and then into the small bowel; that would be fantastic and can be excluded in this case.

The problem of trying to decide what it was that caused a right-lower-quadrant abscess could be very simply solved if it had not been for the evidence of liver damage and common-duct obstruction, which I cannot reconcile with the presence of an abscess in the right lower quadrant. I do not believe that infection from a perforating ulcer gravitated downward; nor do I think pancreatitis did the same thing.

DR. ELLIS: What evidence was there that he had obstructive jaundice?

DR. SWEET: The alkaline phosphatase.

DR. ELLIS: That value was not very high. The stools were not clay colored except for one day.

DR. SWEET: I do not know what was in the upper abdomen except an ulcer. The most common lesion in a man of thirty-five that would explain the acute difficulty is a perforated appendix. Whether he had a liver abscess or an infection of the liver resulting from the appendix that had become necrotic and involved adjacent bowel I do not know, but that could connect the two conditions. In most of these cases the liver abscess or pylephlebitis becomes the major difficulty in the clinical history. Otherwise, I cannot make any further diagnosis.

DR. RICHARD B. COHEN: Dr. Ellis, have you any comment?

DR. ELLIS: This man had a great deal of difficulty with the ulcer before the first admission. He had been advised to have an operation but elected to try medical therapy. The ulcer healed after six weeks of treatment and recurred six months later as demonstrated in the x-ray films that he brought in with him at the time of the first admission. At that time he had had an acute illness for a week, and his physician thought that the ulcer was perforating and ought to be operated on. When he came into the hospital it seemed clear that the illness was infectious hepatitis, for he was jaundiced, he had fever, nausea, vomiting and anorexia, and the liver was tender. To complicate that he had pain and tenderness in the right lower quadrant. That was difficult to explain, and I believed that it was caused by another condition. I could not tie the two together. We thought that he had three diseases — a gastric ulcer, infectious hepatitis and appendicitis. We did not want to operate for appendicitis in the face of hepatitis and therefore elected to treat the hepatitis and treat the appendicitis conservatively. Over the course of two weeks he steadily improved, the jaundice subsided, his appetite returned, and the right-lower-quadrant pain disappeared.

Two months later he walked into my office at five o'clock one afternoon, doubled over and looking acutely ill, and had a spastic abdomen. I thought he had a perforated appendix, and Dr. Frank C. Wheelock operated on him that night with that diagnosis. At the time of operation there was about 25 cc. of clear fluid in the region of the mass that appeared to be an abscess in the region of the cecum and small bowel. This mass was so matted that there was no thought of dissecting it out. It was assumed that there was an ulcerated appendix, and the mass was drained. No exploration was carried out.

DR. JOHN B. MCKITTRICK: Dr. Ellis and I took turns holding each other's hands as we tried to explain the complicated findings in this patient. I thought, when I first saw him, that he had appendicitis and hepatitis in addition to the gastric ulcer. We recognized the hazards of making more than one diagnosis and yet could not get the evidence to explain

the whole picture with one diagnosis. On the third hospital admission, we elected to explore him to determine the nature of the trouble.

Clinical Diagnosis

Appendiceal abscess.

Dr. Richard H. Sweet's Diagnosis

Appendiceal abscess.

Anatomical Diagnosis

Adenocarcinoma of stomach, with metastases to peritoneum and abdominal lymph nodes.

Pathological Discussion

Dr. McKittrick: At operation we found an indurated, fixed mass involving the cecum, the appendix, the terminal ileum and sigmoid. Scattered throughout the abdomen, involving the visceral and parietal peritoneum, were plaques of hard, white-to-grayish tissue. These plaques were found in the hilus of the liver, in the gastrohepatic ligament and around the gastric ulcer. Multiple biopsies for frozen section were obtained, but the pathologist could not confirm our impression of a malignant process. The mass in the right lower quadrant was resected primarily to establish the diagnosis rather than to cure the disease. The gastric ulcer could not be visualized, but was palpated and felt benign.

Dr. Cohen: The surgical specimen consisted of 25 cm. of terminal ileum, cecum, and several centimeters of ascending colon in continuity. The peritoneum was gray, thickened and indurated over the entire specimen, making the bowel stiff and inflexible. Many firm adhesions were present. The appendix was identified retrocecally and was involved in the same process, as was the remaining bowel. No periappendiceal abscess was found. In cross-section the bowel and appendix showed thickened, edematous walls and mucosa. Microscopical examination of the specimen revealed the peritoneum to be diffusely infiltrated by an adenocarcinoma that was poorly differentiated in many areas, with numerous signet-ring cells. An origin in the stomach was suggested.

Several months after the last operation the patient was readmitted to the hospital with an intestinal obstruction, and after six weeks he died in the hospital.

At autopsy a 3-cm. ulcer crater was found on the lesser curvature of the stomach 7 cm. above the pylorus. This proved to be a carcinoma on histologic examination. Lymph nodes were massively involved, and the peritoneum was diffusely infiltrated. Numerous adhesions had resulted in intestinal obstruction, with severe dilatation of the bowel. The liver was fatty but otherwise normal, and the bile ducts were patent and not distended although periportal lymph nodes were replaced by tumor.

Dr. Benjamin Castleman: The absence of tumor in or close to the liver or biliary tract would certainly confirm Dr. Ellis's impression that the jaundice was caused by infectious hepatitis. The facts that this man had ulcer symptoms for three years and that the ulcer had become smaller on an ulcer regimen are not sufficient evidence that this cancer developed on a preexisting benign ulcer. I believe that this gastric lesion originated as a carcinoma and that the peptic ulceration of the cancer was secondary. This case is similar to those reported some years ago by Dr. Tracy B. Mallory.*

*Mallory, T. B. Carcinoma in situ of stomach and its bearing on histogenesis of malignant ulcers. *Arch. Path.* **30**:348-362, 1940.

CASE 41042

Presentation of Case

A seventeen-year-old carpenter's assistant was admitted to the hospital because of nuchal rigidity.

The patient first had a frontal headache and generalized myalgia four days before admission after several days of coryza. These symptoms improved with symptomatic therapy and then recurred with increased severity on the day of admission together with episodes of emesis, a painful neck and a temperature of 102°F. He received 1,500,000 units of penicillin in two doses, after which nuchal rigidity and unequal knee jerks were noted and he was immediately admitted to the hospital.

Physical examination revealed an acutely ill boy complaining bitterly of occipital headache and pain in the eyes from the bright light. There was no evidence of infection of the ears, nose, mastoids or tonsils. There was no cervical adenopathy. The Kernig and Brudzinski reflexes were positive, and there was severe nuchal rigidity. The abdomen was soft, and no masses were felt.

The temperature was 103°F., the pulse 96, and the respirations 22. The blood pressure was 130 systolic, 74 diastolic.

Examination of the blood disclosed a hemoglobin of 12.5 gm. per 100 cc. and a white-cell count of 16,700, with 96 per cent neutrophils. The blood sugar was 115 mg. per 100 cc. The urine was not remarkable. The cerebrospinal fluid contained 4600 cells per cubic centimeter, with 90 per cent neutrophils and 10 per cent monocytes. The protein was 130 mg., and the sugar 78 mg. per 100 cc. The initial pressure was equivalent to 210 mm., and the final pressure to 140 mm. of water. Cultures were negative, and a smear revealed some gram-positive cocci within the cells. Throat culture showed abundant *Neisseria catarrhalis,* moderate growth of *Haemophilus influenzae* and a few diphtheroids.

The patient was immediately started on 500,000 units of penicillin intramuscularly every two hours, 0.5 gm. of chloramphenicol intramuscularly every six

hours, and 2.5 gm. of sulfadiazine intravenously in 5 per cent dextrose and water every six hours; this program was continued throughout the next seven days. The sulfonamide level on the second hospital day was 10.3 mg. per 100 cc. He improved rapidly and on the day after admission was afebrile, with less nuchal rigidity. He complained of minimal headache, nausea, and photophobia.

Six days after admission, while on full antibiotic therapy, he complained of right-lower-quadrant pain, with anorexia and nausea but without vomiting, diarrhea or fever. Examination of the abdomen revealed right-lower-quadrant point tenderness, and rebound tenderness was referred to this quadrant. The psoas-muscle sign was weakly positive. On rectal examination, there was slight right-sided tenderness. The white-cell count rose from 6200 to 11,100, with 71 per cent neutrophils. He had had no bowel movement during the past two days. The local tenderness increased throughout the day, with more right-lower-quadrant spasm. The white-cell count increased to 18,500 three hours later. Urinalysis was negative.

On the seventh hospital day an operation was performed.

Differential Diagnosis

Dr. Lewis W. Kane*: It seems to me that there are two distinct and apparently independent pictures. There is a description of meningitis and a classic picture of acute appendicitis. How, if at all, were these interrelated? That seems to me to be the problem in this discussion.

I believe I must make a diagnosis of bacterial meningitis. In the absence of any cultures to the contrary, entirely on clinical grounds, I believe it was meningococcal meningitis. The patient was sick for several days before he complained of any signs suggestive of meningitis; he had the headache and myalgia commonly seen in the meningococcemic stage before the meningococcus invades the meninges. It is of interest that when invasion occurs, the headaches shift from over the frontal to the occipital area as they did in this case. That the cerebrospinal-fluid sugar was normal on entry is disconcerting, but I believe it can be explained by the fact that the infection was not a severe one and that the diagnosis was made early and therapy was applied without delay. That the cultures were negative is again disconcerting, but they may be negative even in cases of untreated meningococcal meningitis and this patient had received penicillin before entry. What is more disturbing to me is the smear. It is difficult for me to explain why the organisms were gram positive instead of gram negative — if I stick to my diagnosis of meningococcal meningitis. I am not sure that I can explain it except perhaps as a technical error. If, in the performance of a gram stain, decolorization is inadequate, the organisms are likely to be positive rather than negative. On the other hand, it seems to me that when students do gram stains the opposite takes place — they overdecolorize and organisms that should be positive often appear negative. Because that finding does seem out of line in view of the other data I shall disregard it with the knowledge that I am taking a chance in doing so. I do not believe that the patient had a staphylococcal or pneumococcal meningitis. In the first place his response to antibiotics was too dramatic for these other conditions. Moreover, in a pneumococcal meningitis, a spinal-fluid smear is almost always positive and so is the culture.

Six days after the onset of meningitis he complained of symptoms that were unmistakably those of acute appendicitis, and on examination I am sure that diagnosis was confirmed. At least I am certain that the operation was an abdominal operation, and I believe that an acute appendicitis was found.

I have the greatest difficulty in trying to relate the meningitis and the appendicitis. I could take the stand that he had an independent, unrelated acute appendicitis that the antibiotics did not stop. On the other hand, I am tempted to try to discover a relation between the two. My reasoning is somewhat as follows. He had meningococcemia so that infection presumably could have developed in any organ. However, in the cases of meningococcal meningitis complicated by metastatic infection in other organs, the appendix and intestinal tract are very infrequently involved. I believe that the appendicitis was probably not secondary to the bacteremia although it could have been.

The next thought that appeals to me is the possibility that the antibiotics themselves played a part in setting up the conditions that allowed the development of acute appendicitis. We know that antibiotics reduce the number of sensitive organisms in the colon. Resistant organisms, usually *Staphylococcus aureus,* then begin to multiply and may invade, resulting in an enterocolitis of varying severity. It occurs to me that if this reaction were in the neighborhood of the appendix, an acute appendicitis might result.

In summary I believe that the patient had a meningococcal meningitis and acute appendicitis that followed the administration of antibiotics.

Dr. Walter Bauer: I wonder why you are so willing to rule out pneumococcal meningitis. What is wrong with the history? It could respond just as well to the treatment as meningococcal meningitis.

Dr. Kane: It could have been pneumococcal meningitis, but the disease was too mild and the sugar content of the spinal fluid too high for most cases that I have seen. The spinal fluid in cases of meningitis due to pneumococcus usually contains many organisms. It may look like a culture medium, and the sugar is usually quite low.

Dr. Bauer: This patient had not had the menin-

*Assistant in medicine, Massachusetts General Hospital.

geal infection very long before the culture was done, and he had received 1,500,000 units of penicillin.

DR. KANE: I noted that he was treated very early, but even so I should have expected organisms in the spinal fluid. However, I know of a recent patient with proved pneumococcal meningitis who was given one injection of penicillin intramuscularly at an outside hospital and transferred here four hours later. Their culture taken before penicillin therapy was positive whereas ours four hours later was sterile.

DR. PHILIP H. HENNEMAN: Is the intracellular location of the organism significant?

DR. BAUER: It would not be helpful one way or the other. I should bet on pneumococcal meningitis.

DR. KANE: Apparently, that is what the service thought from the treatment given.

DR. LAWRENCE J. KUNZ: We have seen cases of pneumococcal meningitis in which the organisms grew out on culture before therapy but did not after therapy, although pneumococci were still seen in smears of the spinal fluid. This appears to have been the same sort of situation. Apparently, there was some question whether the organisms seen in smears of this patient's spinal fluid were gram-positive or gram-negative cocci.

DR. KANE: Were these smears examined on the ward or in the laboratory?

DR. BENJAMIN CASTLEMAN: In the emergency ward.

DR. KUNZ: The clinicians apparently were not sure since they gave the patient penicillin, chloramphenicol and sulfadiazine.

DR. CASTLEMAN: There is a question mark before the gram-positive cocci. I do not know that we shall be able to settle that.

DR. KANE: I think that the gram stains are less painstakingly done in the emergency ward than in the laboratory.

CLINICAL DIAGNOSIS

Acute appendicitis.

DR. LEWIS W. KANE'S DIAGNOSES

Meningococcal meningitis.
Acute appendicitis, subsequent to antibiotic therapy.

ANATOMICAL DIAGNOSES

(Meningitis.)
Acute appendicitis.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: At operation an acute appendicitis was found. It was a congested, fibrin-coated appendix. The surgeon had no trouble removing it. He took a culture of the serosa of the appendix, which unfortunately showed no growth. Also, unfortunately, when we received the appendix, we did not know the history of the case and did not perform a culture of the contents of the appendix — we do not ordinarily do so in acute appendicitis. Microscopical examination showed marked ulceration of the mucosa, with polymorphonuclear infiltration; the inflammation extended throughout the entire wall and looked like the garden-variety type of acute appendicitis.

One interesting point about this case is that the appendicitis developed in a patient who was on good antibiotic treatment. Some physicians in the past have said that we might be able to treat appendicitis with antibiotics alone. Here is an example of a patient who had been on antibiotic therapy for seven days and yet appendicitis developed.

Although I cannot be sure that Dr. Kane is not correct in suggesting that there was something like the staphylococcal enteritis that follows antibiotic treatment I have never heard of one involving the appendix alone and not other parts of the intestines. The patient went home a week after the operation and returned to the clinic three weeks later feeling perfectly well.

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PATHOGENESIS OF CONGENITAL FAULTS

FOR many years it has been known that older women are more prone to bear mongoloid children than younger women are; a similar trend has been uncovered with respect to hydrocephalus. To the data demonstrating the association of a few specific congenital defects with the aging of mothers evidence is now added that the percentage of malformed fetuses to be encountered in a series of miscarriages also increases with accumulating years of the mother.[1] As with mongolism the strength of the relation becomes most pronounced after the age of thirty-five; between forty and forty-nine all except 1 of 31 embryonic or fetal specimens examined by Hertig and his colleagues[2] were abnormal by pathological diagnosis.[3]

Although the process of aging is too complex to be treated as though "old age" were a pathogenic agent, the measure of years is a useful index of intrinsic social, anatomic and physiologic factors (and pathogenic agents) that cause stresses and strains in the conceptus as well as in parents. Age alone — the mere accumulation of years — is not among the natural forces that can be controlled by man. On the other hand, many of the "slings and arrows of outrageous fortune" that come with time may be guarded against or minimized, especially if the slings can be identified and the trajectories of the arrows determined.

In the field of infectious disease, etiologic understanding (and with it prevention) has come both with refinements in clinical classification — separation of the exanthemas into component subgroups such as measles, scarlet fever and smallpox, for example — and from a more precise grouping and knowledge of pathogenic agents like viruses, bacteria, rickettsias, poisons and vitamin deficiencies. Analogously, in the field of malformations and deaths of prenatal origin progress is to be expected as biologic classifications and knowledge of specific causative mechanisms (hutchinsonian teeth and syphilis, erythroblastosis and Rh antigen antibodies, congenital cataract and rubella) become more precise.

The first step in the direction of a satisfactory solution is nosologic — the identification by objective signs of the disease being studied; it does not suffice to dismiss the death of the conceptus as "abortion" or "miscarriage." Next the complex of causes that bring about such antenatal deaths or fetal deformity is to be analyzed. So viewed (as a complex rather than a cause) advanced maternal age becomes only a point of departure; its real significance is that of an index of disturbances of pregnancy that merely happen to correlate with advancing age. Such a correlation suggests major operations, dietary deficiencies, anemias, leukemias and chronic infections, toxemia and pyelonephritis; endocrine, cholecystic and hepatic disorders; and uterine and placental diseases or hemorrhage. At the moment the clinical value of positive correlation with age is problematical, although vari-

ous other correlations of the past century have proved to be marks of progress. It has proved important in the interests of both prognosis and prevention to know that miscarriages, notched incisor teeth and interstitial keratitis may originate in congenital syphilis, abortions, congenital cataracts and deafness, in maternal rubella during pregnancy, cerebral palsy in prolonged anoxia, and kernicterus in maternal sensitization to the baby's Rh antigen — possibly in combination with anoxia. The tangled skeins are being tediously unraveled. Progress is indeed slow when it is an advance to know that persons who are dead even before they are born deserve the same careful study heretofore reserved for persons who have died after leaving the deceptive security of the maternal organism.

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DIRECTOR OF MEDICAL EDUCATION AND RESEARCH

THE recent appointment of so well qualified a clinician, teacher and investigator as Dr. Mario Stefanini to the newly created post of director of medical education and research at St. Elizabeth's Hospital in Brighton is another example of a forward trend in hospital organization. It is the result of a new awareness on the part of the non-university-connected hospitals of the place that they must occupy in the field of expanding professional responsibilities. It is not so important that by this progressive step St. Elizabeth's Hospital becomes the first of the institutions in its class in the Boston area to add such a position to its top-ranking staff appointments, as that the step is based on a new concept of professional service. For these major hospitals must participate in postgraduate education and in research if they are to attract interns and residents, offer educational facilities to their staffs and provide the best possible medical care for their patients.

It is perhaps because of the very fact that Boston with its three medical schools is a recognized center of medical education that other parts of New England have preceded the metropolis in accepting this evolutionary process. In Connecticut, hospital directors of medical education are already functioning in the Waterbury and Bridgeport hospitals and, in Hartford, in St. Francis Hospital and the Hartford Hospital. The Rhode Island Hospital in Providence and the Worcester City and St. Vincent hospitals in the latter city have also adopted the plan.

The program at St. Vincent is unique in that, in addition to having a director of medical education, a teaching and visiting affiliation has been made with the Georgetown University Medical Center of Washington, D. C. Under this affiliation Dr. Harold J. Jeghers, professor of medicine, serves as consultant in medical education on the St. Vincent staff, other members of the faculty holding comparable consulting positions. Teaching visits, sometimes by guest artists, are arranged, and one resident each year may be rotated through the junior assistant residency at Georgetown.

As part, at least, of the stimulus for these teaching and research programs is the fact that today more hospitals are seeking interns than there are interns available. According to Dr. John C. Leonard, director of medical education in the Hartford Hospital, writing in the March, 1954 issue of the *Journal of the Student American Medical Association,* 6300 medical graduates had in 1953 11,006 approved internships from which to choose. There were, moreover, 22,292 residency appointments available of which only 16,867 were filled in 1952-1953.

In satisfying the educational requirements of these much needed young men and women the hospitals in this category are at the same time benefiting their staffs and raising their standards of service to their patients.

HEALTH IN WATERTOWN IN THE 1630's

LETTERS from the New England Puritan settlement in Massachusetts giving medical information from the East Anglian artisan yeomen, who made up the bulk of the pioneers, to their folks at home are surprisingly few in number. They form, however, an impressive bit of Americana that has survived three centuries, for what is more revealing than an honest letter, with its fresh, impersonal evaluation of the times, the place and the hardships of carving out a bare living from the sparse soil of the land surrounding Massachusetts Bay? The Great Migration to New England of the 1630's was partly the result of hard times in Old England, and there were people in the home country who had many anxieties regarding their sons or neighbors who, surviving the voyage with Governor Winthrop, were setting up a refuge on the rocky coast.

One father, William Pond, of Edwardstone, Suffolk, had two sons in Massachusetts in 1630, one of whom wrote home in March, 1631, describing the discouraging winter that had just passed in Watertown, letting his father know "what a cuntrey theis new Eingland is whar we liue." He goes on to say, "her ar but fewoe eingeines and a gret sorte of them deyeid theis winture it wase thought it wase of the plage," referring to the well known decimation of the Indians by an epidemic, the nature of which is not clear. But the English too were not immune to disease, for Pond continues: "Peple her ar subgecte to deicesesse for her haue deyeid of the skurueye and of

the bur[n]inge feuer too hundreid and ode." No wonder he thought that "the cuntrey is not so as we ded expecte it" and begged his father to send over cloth, "a ferckeine of buttr and a hogseit of mault" and other provisions since "we do not know how longe we may subeseiste for we can not liue her witheought prouisseyones from ould eingland."

Terrible as the first winter must have been, the voyage over was even worse. Pond wrote, "we ware wondurfule seick as we cam at sea withe the small Poxe no man thought that I and my leittell cheilld woolld a liueid and my boye is lame and my gurell too and thar deyeid in the sheip that I cam ine xiiij parsones."[1]

By 1633 conditions had improved considerably; a letter, which has just come to light in 1954, from another resident of Watertown, William Hammond, indicates the striking change in the health of the pilgrims. Hammond, a former tenant of Sir Simonds D'Ewes, one of the promoters of the New England enterprise, wrote to Sir Simonds on September 26, 1633, having emigrated on the *Arbella* in 1630.[2] Three years later he could report that "we haue non seicke her" and that Massachusetts was a country with good harbors, "much champine ground," or open land suitable for tillage, with fresh and salt water fish in abundance, particularly cod, mackerel, and "holy back" (halibut); and such "foul" as ducks, teal, swans, cranes, heath hens and other New England game birds in this sportsman's paradise of the seventeenth century. In a remarkably short time the colonists of Hammond's type learned to live off the country, something that Pond does not seem to have envisaged, with his repeated plea for "prouisseyones from ould eingland," and Hammond went after the striped bass and the "gret stor of heth fesantes" (now extinct since the sole survivor disappeared from observation in the spring of 1932 on Martha's Vineyard).

With fish and fowl, the avitaminosis, "the skurueye" of Pond's day, seems to have disappeared on land, but John Winthrop's warning to his wife to "remember to bringe iuice of Limons to sea with thee" was still held as sound advice up to the time of James Lind's *Treatise of the Scurvy* (1753) and unfortunately for a hundred years or more after its publication.

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BRIDGING THE GAP

On Wednesday, February 9, at 9 p.m. in Boston's Hotel Statler, the American Medical Association, in co-operation with Smith, Kline and French Laboratories, will present a one-and-a-half-hour closed-circuit televised medical postgraduate discussion and clinical demonstration of coronary-artery disease.

Thirteen leading cardiologists representing nine sections of the country (4 of them are from Boston) will talk to an estimated audience of 18,000 physicians in 31 cities — the largest television audience of its kind. This impressive and geographically distributed array of medical talent being made available at one time to physicians within or near their own communities brings home dramatically the tremendous possibilities of television as a scientific educational tool.

It is not difficult for one to conjure up visions of closed-circuit television among medical-research laboratories throughout the country, bridging a gap that in the past has resulted often in duplication that might have been avoided if each had been aware of the others' activities. Closed-circuit telecasts among the medical schools for an interchange of talent and ideas and to bridge the gap of regionalism is certainly now more than a possibility.

It may be only a matter of time before every physician will be able to avail himself of the latest in medical science merely by turning on his own television set at a prescribed hour. Until this possibility becomes a reality, — and it appears at present to be the ultimate in making postgraduate medical education easily available to the busy physician, — it is suggested that physicians take advantage of such productions as the February 9 presentation, to which all are cordially invited.

Some cases of retention from obstinate stricture, requiring puncture through the rectum, have ended fatally, lately, in hospitals.

Boston M. & S. J., *Jan. 31, 1855*

MASSACHUSETTS MEDICAL SOCIETY

WELFARE PROBLEM

The following requirements of the Department of Public Welfare regarding notification are presented for the convenience of physicians practicing in the Commonwealth.

Physicians may provide two treatments in any one month for an acute illness to a patient receiving public assistance without notifying the board of public welfare. The bill for one or two visits in a calendar month must be submitted before the fifteenth day of the following month. If more than two visits are needed for this illness, the physician should notify the local board of public welfare verbally or in writing, and the agency will immediately send the authorization for the total care needed for this illness.

Physicians treating patients receiving public assistance for documented chronic illness are authorized to make four visits a month. A written report is required from the physician every three months. When additional visits are necessary during the course of any one month, whether for the chronic illness or for an acute illness, any visits beyond four will require prior authorization. Bills supported by a copy of the authorization should be submitted to the local board of public welfare before the fifteenth of the month following the month in which the medical services were rendered.

Physicians rendering medical service in excess of two visits during long week ends or holidays should notify the local board of public welfare on the first working day of the local agency, and authorization for such emergency care and any continuing care will be forwarded immediately by the local board.

This method of procedure has been approved by the Department of Public Welfare.

HOWARD P. KENNEDY, M.D., *Acting Chairman*
Committee on Welfare Problems

DEATHS

INGALL — Morris Ingall, M.D., of Newton, died on January 9. He was in his fifty-seventh year.

Dr. Ingall received his degree from Harvard Medical School in 1928. He was a member of the staffs of the Beth Israel Hospital and the New England Medical Center, a fellow of the American Academy of Pediatrics and the American Medical Association and a member of the New England Pediatric Society.

He is survived by his widow, two daughters, a son, a sister and a brother.

KUBIN — Ludwig Kubin, M.D., of Waltham, died on December 18. He was in his sixty-third year.

Dr. Kubin received his degree from the Medizinische Fakultät der Universität, Vienna, in 1920.

He is survived by his widow.

NEVERS — Harry H. Nevers, M.D., of Lawrence, died on December 29. He was in his seventy-ninth year.

Dr. Nevers received his degree from Bowdoin Medical School in 1903. He was consulting surgeon, Lawrence General Hospital, a fellow of the American Medical Association, formerly, president, Essex North District Medical Society, and a member of the Greater Lawrence Medical Association.

He is survived by his widow, a sister and a brother.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

ORTHOPEDIC CLINIC	DATE	CLINIC CONSULTANT
Gardner	February 1	Carter R. Rowe, M.D.
Haverhill	February 2	William T. Green, M.D.
Greenfield	February 3	Charles L. Sturdevant, M.D.
Salem	February 7	Paul W. Hugenberger, M.D.
Brockton	February 10	George W. Van Gorder, M.D.
Lowell	February 11	Albert H. Brewster, M.D.
Worcester	February 11	John W. O'Meara, M.D.
Lynn*	February 14	Daniel M. Killoran, M.D., and John J. Crowley, M.D.
Springfield	February 15	James D. Fisher, M.D.
Pittsfield	February 16	Edward J. Coughlin, Jr., M.D.
Hyannis	February 24	Paul L. Norton, M.D.
Fall River	February 28	David S. Grice, M.D.

RHEUMATIC-FEVER CLINIC	DATES
North Reading	February 1, 8, 15
Fitchburg	February 2, 9, 16, 23

PLASTIC CLINIC	HELD	CONSULTANT
Eastern Massachusetts	Semi-monthly	Bradford Cannon, M.D.
Western Massachusetts	Monthly	Joseph M. Baker, M.D.

Physicians referring new patients to clinic should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

*This clinic serves Lynn, Lynnfield, Saugus, Nahant, Revere, Chelsea, Everett and Winthrop. Referrals should be made directly to the Lynn Clinic.

CORRESPONDENCE

REGARDING COGAN'S SYNDROME

To the Editor: In a keen analysis of our paper, "Nonsyphilitic Interstitial Keratitis and Bilateral Deafness (Cogan's Syndrome) Associated with Essential Polyangitis (Periarteritis Nodosa)" (*New Eng. J. Med.* 248: 1001, 1953), Dr. Emanuel Rosen, who described the sixth case of this syndrome, commented, in a letter in the November 25, 1954, issue of the *Journal*, on the pathogenesis of the condition. Apparently reading between the lines, he states that "many self-incriminations seem evident" on our part because there is "at least a suspicion" that the periarteritis nodosa was "physician induced" by the overuse of antibiotics. If he had read the lines themselves more carefully, he would have concluded that such an evidence does not exist at all. Intensive treatment with penicillin was started only when the patient was admitted to the hospital for the third time with fever and when a streptococcus was cultured from the blood. The angiitis appeared at about the same time, much too early to have been caused by the antibiotic. Moreover, the vascular lesions subsided while the patient was on penicillin. It is true that a short course of chloramphenicol treatment had been given on the outside about five weeks before this admission, but this drug has not been implicated in the production of polyangiitis. The bacteriemia and bacteriuria in our case made a treatment with antibiotics imperative.

Dr. Rosen believes that no antibiotics should be administered unless necessary. With this we agree. Our group had adopted this principle even before 1951, when the representative paper on this subject, to which he refers, was published.

In Dr. Rosen's opinion the case observed by him was viral; our patient had "nothing more than a Ménière syndrome and a keratitis" both of which he labels allergic. The terms "viral" and "allergic" should really denote a specific pathogenesis. Frequently and conveniently, however, they are misused as synonyms for "unknown." In this respect his statements are as vague as his proofs of a definite etiology. That polyangiitis may occur from other causes than hypersensitivity has been proved conclusively.

Dr. Rosen suspects that the rash on our patient's face was due to novocain and that the infected tooth was on the left side. In fact, no novocain was used at that time, and the infected tooth was on the right. It had been successfully treated before the first admission.

In his final, somewhat prophetic statement Dr. Rosen expresses the belief that any case of Cogan's syndrome could be converted into the clinical picture of periarteritis nodosa by the use of "hypersensitizing drugs." The fact remains that no cases have yet been converted.

MATTHEW TAUBENHAUS, M.D.

Chicago, Illinois

SUCCESSFUL REHABILITATION

To the Editor: In 1930 E. W. W., a twenty-four-year-old left-handed man, sustained a 10-cm. horizontal, right temporoparietal fracture of the skull in an automobile accident in the mountains. It was seventy-two hours before he was hospitalized with convulsions. No major surgical interference was undertaken. From 1931 to 1935 sequelae included impairment of speech, vision and balance; there was anomic motor aphasia, homonymous hemianopsia and not one, as had been at first reported, but two dead labyrinths without appreciable loss of hearing, demonstrating destruction of areas in the central nervous system. Peripherally, the eyes presented choroiditis, inability to recognize colors with either eye and numerous scotomas large and small. Tests by ophthalmologists and otolaryngologists for malingering, including tests for hysterical spasm of vocal cords, were negative. Re-education was conducted under the daily supervision of a physician who was a neurologist and psychiatrist. (Recently, a highly specialized work—*Aphasia Therapeutics,* by Mary Coates Longerich and Jean Bordeaux — became available to those who understand such terms as "geometric-optic agnosia.") Throughout 1931 and 1932 no improvement was apparent, but by 1935 improvement had become observable and rapid. Despite periodic attacks of anomia, defective vision and cerebellar gait, the patient had obtained employment as an orderly in the Albany Hospital.

This case gives evidence that some employers of the handicapped recognize the importance of the dominating interest of the patient. The hospital authority said, "Here is a list of departments that can use an orderly. Visit around for a day or two, thinking of each, and let us know in which you prefer to work." The father of the patient and his son each held main focus of attention on electric phenomena; therefore choice of the Department of Radiology was clear cut. In 1936 and 1937, the hospital having recommended him for study in the X-Ray Division of the General Electric Company, he became a registered technician and as such returned to radiology in Albany. Steady improvement thereafter is evident from observation of promotions. In 1938 he was appointed chief technician in the Department of Radiology, in 1940 director of the newly organized School for Technicians there and in 1953 associate in radiology in the Albany Medical College.

Handedness may be of interest. Before the fracture of the skull, this left-handed man could write with either hand, preferring the left, and two years later with either hand, preferring the right. The late Sir Charles Scott Sherrington (1859-1952) investigated the theory that cerebral dominance might be indicated by contrary handedness and, secondly, that nerve tissue once destroyed might not regenerate but that in time new tracts might be developed. In 1943, while World War II was depleting hospital staffs, the patient devoted his nights to inventing his method, now universally used, for protecting patients from overexposure during radiation therapy. During that work he was exposed to an x-ray burn. Because the duration and intensity of exposure were accurately known, his injury offered unique opportunities for scientific study. Chance had long been sought to record every stage of the progressive deterioration of exactly this type of lesion. Therefore, taking counsel with no one, he decided that he would bear the pain involved, with the purpose of retaining the limb as long as possible to permit scientific observation, color photography and the compilation of the data desired and thus to help specialists improve their treatment of all radiation burns in the future. To this end he refused amputation until the sixth month, when gangrene had set in. Amputation of the right forearm just below the elbow forced absolute resumption of the original left-handedness. Thus, if there is cerebral dominance, there is ability to reverse it, not merely once but twice. In 1954 the patient was observed while playing a piano, utilizing the little finger of his prosthesis to manipulate keys at the far end of the keyboard.

Poor vision presents the most long continued of the serious sequelae. Large and small multiple residual scotomas led to the prescription of telescopic lenses for reading, between 1948 and 1952. With their use the eyes improved more than had been anticipated, and thereafter the patient voluntarily abandoned the telescopic — to return to the more conventional bifocal — spectacles. In 1953 headaches accompanied with flashes of lightning moving outward and upward in the visual field still troubled him, but by 1954 they had lessened so that he refused re-examination.

The foregoing abstract suggests data available for practical application in approximately similar cases. These data can be turned to profit when one needs something to encourage the relatives of patients to see that the injured attend to treatment, follow a schedule of constant re-education and patiently anticipate improvement that good care may manifest five or more years after serious head injuries. Relatives, neurologists, psychiatrists, rehabilitation agencies and finally the employers of the handicapped occupy, *ad seriatim,* unique positions demanding sustained fortitude to restore to fine efficiency patients presenting serious sequelae after skull fractures.

SARAH PARKER WHITE, M.D.
Boston

REVOCATION OF LICENSE

To the Editor: At the meeting of the Board of Registration in Medicine held December 16, 1954, it was voted to revoke the registration of Dr. Eustace A. Carmichael, of Worcester, Massachusetts.

ROBERT C. COCHRANE, M.D.
Secretary
State House
Boston

NONCLINICAL NOTES

ASSOCIATION FOR RESEARCH IN NERVOUS AND MENTAL DISEASE

The Association for Research in Nervous and Mental Disease announces the election of the following officers for the coming year: president, Dr. J. E. Moore; first vice-president, Dr. John Romano; second vice-president, Dr. David Seegal; secretary-treasurer, Dr. Clarence C. Hare; and assistant secretary, Dr. Rollo J. Masselink.

NOTICES

ANNOUNCEMENTS

Dr. David F. Freeman announces the opening of his office at 17 Prospect Street, Waltham, for the practice of psychiatry.

Dr. Timothy A. Lamphier announces the removal of his office from 478 Commonwealth Avenue to 30 Fenway, Boston, for the practice of surgery.

VIDECLINIC

Videclinic — a special closed-circuit television program designed to bring new advances in medicine to physicians quickly—will have its coast-to-coast premiere on February 9, under the sponsorship of the American Medical Association.

Physicians of Boston and environs are invited to view the presentation in the ballroom of the Hotel Statler in Boston at 9 p.m. on Wednesday, February 9. This first program, running for an hour and a half, live, closed circuit, black and white, theater-size screen, will be a medical postgraduate discussion and clinical demonstration of coronary-artery disease.

Four of the 12 specialists participating in the Videclinic are from Boston: Dr. Herrman L. Blumgart, professor of medicine, Harvard Medical School; Dr. Howard B. Sprague, associate professor of clinical medicine, Harvard Medical School; Dr. Fredrick J. Stare, professor of medicine, Harvard School of Public Health; and Dr. Paul D. White, professor of medicine, Harvard Medical School.

Over 18,000 physicians in 32 cities are expected to view this telecast. Produced by Smith, Kline and French Laboratories, the program will bring the full array of modern television technics — live television, "remote pickups" from medical centers and adequate film coverage.

NEW ENGLAND CARDIOVASCULAR SOCIETY

A meeting of the New England Cardiovascular Society will be presented by the Beth Israel Hospital and the Massachusetts Memorial Hospitals in Morse Auditorium, Museum of Science, Boston, on February 7 at 8 p.m.

The program is as follows:

Beth Israel Hospital. Dr. Herrman L. Blumgart, presiding.

The Effect of Induced Hypothyroidism on the Serum Lipoproteins of Patients with Intractable Angina Pectoris and Congestive Heart Failure. Drs. George S. Kurland, George V. Mann and A. Stone Freedberg.

Effects of Sympathomimetic Drugs on Ventricular Rhythmicity and A-V Conduction: Studies during treatment of Stokes–Adams disease with an electric cardiac pacemaker. Drs. Paul M. Zoll, Arthur J. Linenthal, Leona R. Norman, Milton H. Paul and William Gibson.

Acute Peripheral Arterial Occlusion: A basis for its clinical management. Drs. Stanford Wessler and Marvin Gilbert.

Massachusetts Memorial Hospitals. Dr. Robert W. Wilkins, presiding.

Functional Histochemistry of the Digital Arterial-Venous Anastomoses (Glomus). Drs. Harry J. Hurley, Jr., and Herbert Mescon.

Responses of Energy Metabolism in Congestive Heart Failure. Dr. William E. Huckabee.

Some Observations on Venous Tone of the Limbs in Congestive Heart Failure. Dr. J. Edwin Wood, Julius Litter, Irwin H. Friedman and Robert W. Wilkins. Interested physicians and medical students are invited.

HARVARD MEDICAL SOCIETY

A meeting of the Harvard Medical Society will be presented by the Department of Obstetrics of the Boston Lying-in Hospital and the Free Hospital for Women, with Duncan E. Reid, presiding, in the auditorium, Boston Lying-in Hospital, on Tuesday, February 8 at 8 p.m.

The program is as follows:

Some Metabolic Effects of Oxytetracycline. O. Watkins Smith and Charles C. Roby.

Contribution of Maternal Iron (Isotopically Identified) to Blood Formation during Infancy. Clement A. Smith, Ruth B. Cherry, Costa J. Maletskos, Charles C. Roby, John G. Gibson and Duncan E. Reid.

Effects of Anoxia on Metabolism in the Fetus and Newborn. Claude A. Villee and Ruth Kimmelstiel.

Application of Physiologic Technics to Respiratory Disturbances of the Newborn Infant. Charles D. Cook, Ruth B. Cherry, James M. Sutherland, Sydney Segal and Clement A. Smith.

Measurements of Uterine Blood Flow in Human Term Pregnancy. James Metcalfe, Seymour L. Romney, Duncan E. Reid and C. Sidney Burwell.

Effects of Posterior Pituitary Extracts on Electrolyte Excretion. Howard N. Jacobson.

TUFTS MEDICAL ALUMNI ASSOCIATION LECTURE

Dr. John F. Conlin, medical director of the Boston City Hospital, will deliver the annual medical-alumni lecture, entitled "Medicine, Men and Money," at Tufts College Medical School on Tuesday, February 15 at 4 p.m.

Medical students and physicians are invited.

AERO MEDICAL ASSOCIATION

The twenty-sixth annual meeting of the Aero Medical Association will be held at the Hotel Statler, Washington, D. C., March 20 through 23.

INTERNATIONAL COLLEGE OF SURGEONS

The Mid-Atlantic Division regional meeting of the United States Section of the International College of Surgeons will be held at the Statler Hotel, Washington, D. C., on February 11 and 12. There will be a luncheon each day, and a banquet, preceded by a social hour, will be held on the evening of February 11.

The Southwestern Division regional meeting of the United States Section of the College will be held at the Shamrock Hotel, Houston, Texas, February 28 to March 1. There will be a luncheon each day and a banquet, preceded by a social hour, on the evening of February 28.

NEW YORK ACADEMY OF SCIENCES CONFERENCE ON RESERPINE

A conference on reserpine in the treatment of neuropsychiatric, neurologic and related clinical problems will be held under the auspices of the Section of Biology of the New York Academy of Sciences at the Barbizon-Plaza Hotel, New York City, February 3 and 4. Attendance is limited to invited participants and members of the Academy.

AMERICAN CONGRESS OF PHYSICAL MEDICINE AND REHABILITATION

The thirty-third annual scientific and clinical session of the American Congress of Physical Medicine and Rehabilitation will be held at the Hotel Statler, Detroit, August 28 through September 2.

The scientific sessions and instruction seminars are open to physicians and registered therapists. Further information may be obtained from the executive secretary, Dorothea C. Augustin, American Congress of Physical Medicine and Rehabilitation, 30 North Michigan Avenue, Chicago 2, Illinois.

SECOND INTERNATIONAL CONGRESS OF ALLERGOLOGY

The Second International Congress of Allergology will be held, by invitation of the Brazilian Allergy Society, in Rio de Janeiro, November 6-13, under the chairmanship of Dr. F. W. Wittich, of Minneapolis, Minnesota, president of the International Association of Allergology. An extensive program dealing with almost all important problems of allergy and related immunology, biochemistry, pharmacology and therapeutics is under preparation.

Sir Henry H. Dale, of London, Professor Pasteur Vallery-Radot, of Paris, Professor Bernardo Houssay, of Buenos Aires, and Dr. Robert Cooke, of New York City, have been invited as guest speakers. The official languages will be English, French, Portuguese and Spanish, and the main topics will be presented in these languages, although scientific communications and discussions may be presented in the native language of the author.

A fairly large number of scientific communications will be presented.

North Americans wishing to present papers should send their requests to Dr. Fred W. Wittich, 424 LaSalle Medical Building, Minneapolis 2, Minnesota.

All information concerning the Congress is available from the General Secretary, Dr. Bernard N. Halpern, 197. Boulevard Saint Germain, Paris VII°, France, and from the Secretary of the Sociedade Brazileira de Alergia, Dr. Fabiano Alves, Avenida Rio Branco 277, 7° andar, sala 705, Rio de Janeiro, Brazil.

HEMOPHILIA FOUNDATION FELLOWSHIP IN HEMATOLOGY

The national office of the Hemophilia Foundation announces the establishment of a fellowship in hematology at the Mount Sinai Hospital in New York City. This award is intended to provide opportunity to interested physicians for detailed clinical and laboratory study in disorders of coagulation. The fellowship of $3,600 will be awarded annually, the first fellowship to begin as of July 1, 1955. Further information may be obtained from the Medical Secretary, Hemophilia Foundation, 60 East 42d Street, New York, New York.

AMERICAN CONGRESS OF PHYSICAL MEDICINE AND REHABILITATION ESSAY AWARD

The American Congress of Physical Medicine and Rehabilitation announces an annual award of $200 for the best essay, not exceeding 3000 words, on any subject pertaining to physical medicine and rehabilitation.

The competition is open to anyone, but directed primarily to medical students, interns, residents and graduate students in preclinical sciences and physical medicine and rehabilitation.

Manuscripts should be submitted as original and one carbon copy, not previously published, before June 1, 1955, to the American Congress of Physical Medicine and Rehabilitation, 30 North Michigan Avenue, Chicago 2, Illinois.

MEDICAL LIBRARY ASSOCIATION SCHOLARSHIPS

The Medical Library Association offers four scholarships of $150 each for summer-school courses in medical library work in 1955, two at Columbia University and two at Emory University.

Applications for the scholarships should be made to the school at the time of application for enrollment and as soon as possible, enclosing a transcript of academic records. No applications for scholarships will be accepted after April 1, 1955. Completion of either course will enable a student who has a bachelor's degree and a year of library-school training to qualify for Grade 1 certification by the Medical Library Association.

SOCIETY MEETINGS AND CONFERENCES

FEBRUARY–APRIL. Postgraduate Medical Institute. Page 451, issue of September 9.

FEBRUARY–MAY. Sanitary Engineering Center Training Programs. Page 122, issue of July 15.

FEBRUARY 1 and 15. New England Deaconess Hospital Lectures. Page 993, issue of December 9.

FEBRUARY 1–23. Consultation Clinics for Crippled Children in Massachusetts. Page 155.

FEBRUARY 3 and 4. New York Academy of Sciences Conference on Reserpine. Page 157.

FEBRUARY 4. New England Society of Anesthesiologists. Page 1075, issue of December 23.

FEBRUARY 4 and APRIL 8. Massachusetts Society for Research in Psychiatry. Page 679, issue of October 14.

FEBRUARY 5–MAY 7. Middlesex South District Medical Society. Postgraduate Course. Page 758, issue of October 28.

FEBRUARY 7. New England Cardiovascular Society. Page 157.

FEBRUARY 7–9. McIntyre–Saranac Conference. Page 410, issue of September 2.

FEBRUARY 7–MAY 9. Seminar in Psychiatry and Neurology. Page 452, issue of September 9.

FEBRUARY 8. Harvard Medical Society. Page 157.

FEBRUARY 9. Videclinic. Page 156.

FEBRUARY 11 and 12. International College of Surgeons. Page 157.

FEBRUARY 11–25. Pan-American Academy of General Practice. Page 496, issue of September 16.

FEBRUARY 11–MARCH 25. Postgraduate Course in Occupational Medicine. Page 922, issue of November 25.

FEBRUARY 15. Tufts Medical Alumni Association Lecture. Page 157.

FEBRUARY 26 and 27. Mid-Winter Radiologic Conference. Page 1076, issue of December 23.

FEBRUARY 28–MARCH 1. International College of Surgeons. Southwestern Division Regional Meeting. Page 157.

FEBRUARY 28–MARCH 2. American Orthopsychiatric Association. Page 994, issue of December 9.

MARCH 7–12. Course in Care of Atomic Casualties. Page 285, issue of August 12.

MARCH 20–23. Aero Medical Association. Page 157.

MARCH 23–26. International Academy of Proctology. Page 876, issue of November 18.

APRIL 21 and 22. New York Academy of Medicine (Eastern States Health-Education Conference). Page 922, issue of November 25.

MAY 4 and 5. American Psychosomatic Society. Page 286, issue of August 12.

MAY 17–19. Massachusetts Medical Society. Annual Meeting. Hotel Statler, Boston.

JUNE 5 and 6. American Board of Physical Medicine and Rehabilitation. Page 794, issue of November 4.

JUNE 21–25. National Association for the Prevention of Tuberculosis. Page 540, issue of March 25.

AUGUST 28–SEPTEMBER 2. American Congress of Physical Medicine and Rehabilitation. Page 157.

NOVEMBER 6–13. Second International Congress of Allergology. Page 157.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, FEBRUARY 3

THURSDAY, FEBRUARY 3

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*8:45–9:45 a.m. Cardiac Grand Rounds. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.

*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.

*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.

*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*11:00 a.m. Thoracic Conference. The Management of Angina Pectoris. Dr. Dwight Harken. Main Amphitheater, Peter Bent Brigham Hospital.

*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.

*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.

*12:00 m.–1:00 p.m. Surgical Staff Conference. Sherman Auditorium, Beth Israel Hospital.

*12:15–1:15 p.m. Tumor Clinic. The Potential of Radiation Therapy in Approach to Malignant Disease. Dr. James Dealy. Amphitheater, Peter Bent Brigham Hospital.

*4:00–5:00 p.m. Pediatric Seminar. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.

FRIDAY, FEBRUARY 4

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.

*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*11:00 a.m.–1:00 p.m. Medical Grand Rounds. Dr. Proger and Staff. Stearns Auditorium, New England Center Hospital.

*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.

*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.

*4:00–5:00 p.m. Child Psychiatry. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.

*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Waltham Street.

SATURDAY, FEBRUARY 5

*8:00 a.m. Gynecological Grand Rounds. 6th-floor conference room. Carney Hospital, 2100 Dorchester Avenue, Dorchester.

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*8:00–9:00 a.m. Anesthesia Conference. Dr. Etsten. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.

*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.

*9:00–10:30 a.m. Surgical Grand Rounds. Dr. Child and Staff. Stearns Auditorium, New England Center Hospital.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*10:30–12:00 m. Middlesex South District Medical Society. Post-Graduate Course. Congestive Heart Failure. Drs. Howard B. Sprague and Arnold S. Relman. Margaret Jewett Hall, Mount Auburn Hospital, Cambridge.

*11:00 a.m.–12:00 m. Hematology Clinic. Dr. William Dameshek. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.

MONDAY, FEBRUARY 7

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Problems. New England Deaconess Hospital.

*8:30–9:30 a.m. Clinic by Entire Surgical Staff and Anesthesia Staff. Cheever Amphitheater, Dowling Building, Boston City Hospital.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*12:00 m.–1:00 p.m. Clinicopathological Pediatric Conference. Drs. MacMahon and Baty. Pratt Lecture Hall. Joseph H. Pratt Diagnostic Hospital.

*12:00 m.–1:00 p.m. Metabolism Conference. Dr. Schwartz. Stearns Auditorium, New England Center Hospital.

*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.

*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.

*4:00 p.m. Clinicopathological Conference. Pathology Conference Room, Beth Israel Hospital.

*4:00–5:00 p.m. Surgical Pathology. Dr. MacMahon. Stearns Auditorium, New England Center Hospital.

*4:00–5:30 p.m. Anesthesiology Conference. Circulatory Effects of Spinal Anesthesia. Dr. Vandam. Peter Bent Brigham Hospital.

*5:00–6:30 p.m. Anesthesia Group of the Lahey Clinic. Joslin Auditorium, New England Deaconess Hospital.

*7:00–8:00 p.m. Pathology Conference. Dr. MacMahon and staff. Stearns Auditorium, New England Center Hospital.

*8:00 p.m. New England Cardiovascular Society. Morse Auditorium, Museum of Science, Boston.

TUESDAY, FEBRUARY 8

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*12:00 m. Pediatric Grand Rounds. Cheever Amphitheater, Dowling Building, Boston City Hospital.

*12:00 m.–1:00 p.m. Pediatric Combined Rounds. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.

(Concluded on page xxi)

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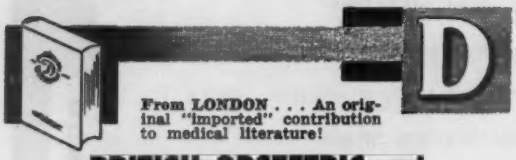

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Levin, S. J. Ped. Cl. of N. A. 1:975,1954.

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Naterman, H. L. The Journ. of Allergy. 24:60,1953.

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Unger, A. H. and Unger, L. Annals of Allergy. 10:128,1952.

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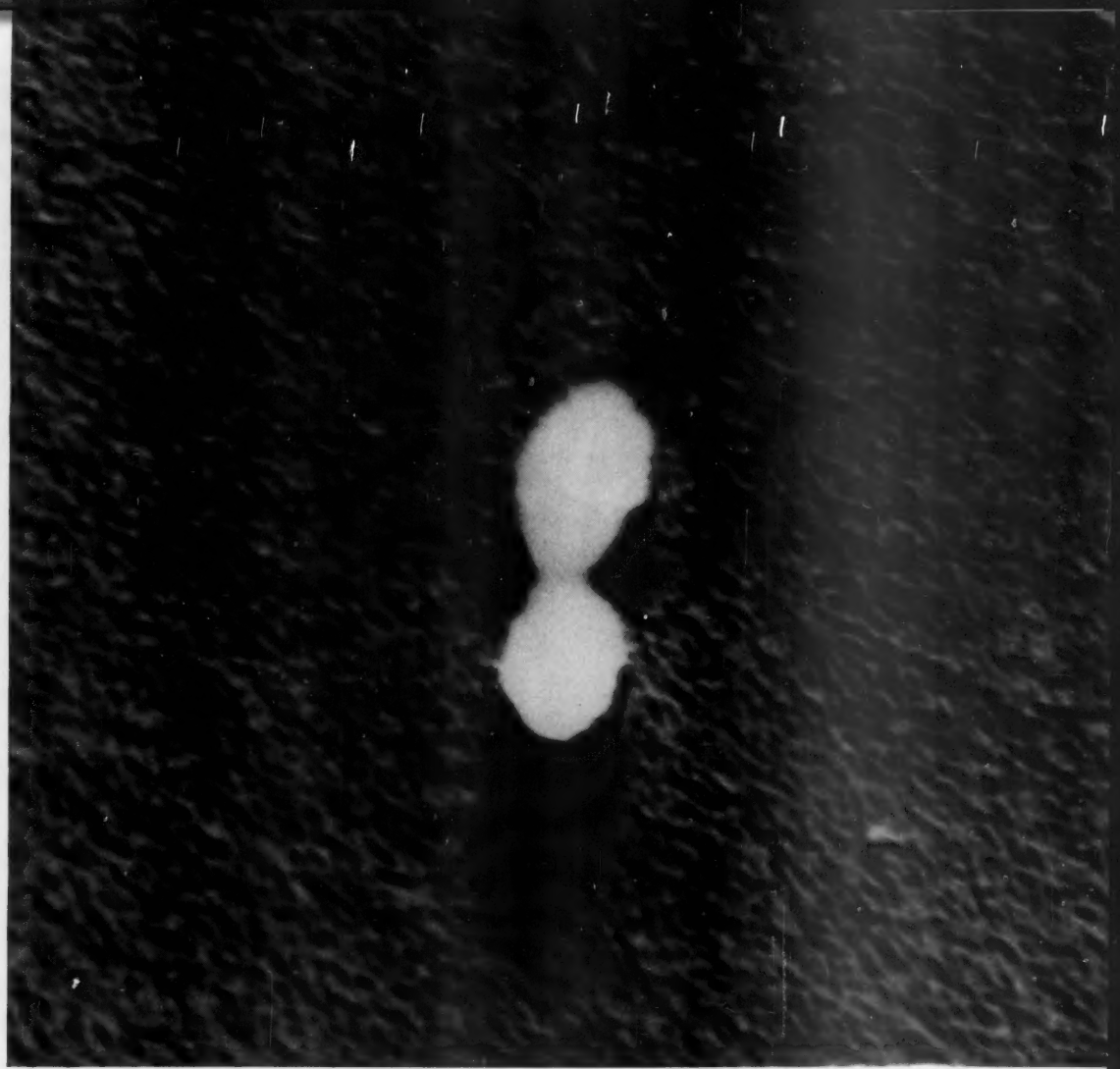

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(Concluded from page 158)

*12:00 m.–1:00 p.m. Endocrine Clinic. Dr. Astwood. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. X-Ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
12:30–1:30 p.m. Medical Journal Club. Joslin Clinic. New England Deaconess Hospital.
*4:00–5:30 p.m. Anesthesia Conference. Dr. Etsten. Stearns Auditorium, New England Center Hospital.
*5:00 p.m. Surgical Journal Review. Mount Auburn Hospital, Cambridge.
*5:00–6:00 p.m. Service Meeting Followed by Clinical Conference (Medical, Surgical, Obstetrical). Faulkner Hospital.
*7:00 p.m. Modern Aspects of Visceral Lupus Erythematosus. Dr. I. Snapper. New Cheever Amphitheater, Dowling Building, Boston City Hospital.
*8:00 p.m. Harvard Medical Society. Boston Lying-in Hospital.

WEDNESDAY, FEBRUARY 9
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m. Orthopedic Grand Rounds. Bigelow Amphitheater, White 3A, Massachusetts General Hospital.
*12:00 m. Boston State Hospital. Psychiatry Seminar. Short-Term Therapy. Dr. Greta Bibring. Reception Building Auditorium, 591 Morton Street, Dorchester.
*12:00 m.–1:00 p.m. Clinicopathological Conference. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*12:00 m.–1:00 p.m. Roentgen Diagnostic Conference. 5th-floor teaching unit, Beth Israel Hospital.
*12:15 p.m. Vascular Rounds. Drs. Edward A. Edwards and Chilton Crane. D-Main, Peter Bent Brigham Hospital.
*12:30 p.m. Weekly Pathological Meeting. Joslin Auditorium, New England Deaconess Hospital.
12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*1:00 p.m. Massachusetts General Hospital Hand Clinic. The Clinics of the Massachusetts General Hospital.
*2:00 p.m. Rectal Clinic. Peter Bent Brigham Hospital.
*2:00–3:00 p.m. Pediatric Conference for Practitioners. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.
*4:00–6:00 p.m. Overholt Thoracic Conference. Joslin Auditorium, New England Deaconess Hospital.
*6:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*7:30–9:30 p.m. Lahey Clinic Lecture. Joslin Auditorium, New England Deaconess Hospital.
*9:00 p.m. Videclinic. Ballroom, Hotel Statler, Boston.

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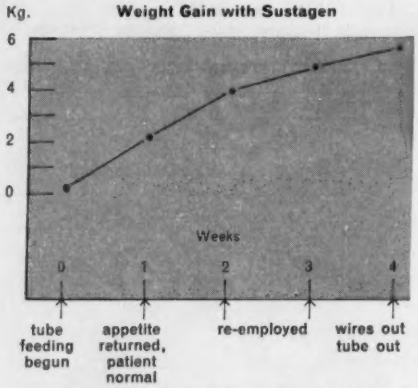

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Niacinamide	100 mg.
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Pyridoxine hydrochloride	5 mg.
Choline bitartrate	500 mg.
Folic acid	2.5 mg.
Vitamin B_{12} (crystalline)	4 mcg.
Iron (from ferrous sulfate)	15 mg.
Calcium	6.3 Gm.
Phosphorus	4.5 Gm.
Sodium	1.9 Gm.
Potassium	7 Gm.

Dilution for tube feeding:
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†Therapeutic Nutrition, Publication No. 234, National Research Council.

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Sustagen makes a pleasant tasting food drink. It can be used as a complete liquid diet or as a concentrated diet supplement for patients who cannot, or will not, take enough ordinary foods to meet their needs.

*Pareira, M. D.; Conrad, E. J.; Hicks, W., and Elman, R.: J.A.M.A. 156: 810, 1954.

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